Community-Driven Research in the Canadian Arctic: Investigating the Effect of Dietary Exposure to Methylmercury on the Severity of Chronic Inflammation and Gastric Neoplasia in Populations with an Elevated Risk of Gastric Cancer

by

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Abstract

Introduction

While gastric cancer has been declining in incidence for decades globally, it remains a major cause of death. Evidence suggests that Indigenous populations worldwide experience a higher burden of gastric cancer relative to non-Indigenous populations residing in the same geographic areas. Within Canada, community-driven research conducted by the Canadian North *Helicobacter pylori* (CAN*Help*) Working Group in western Arctic communities demonstrates a higher burden of gastric disease relative to multi-ethnic populations in southern regions. CAN*Help* community projects use community input to guide research aiming to address this disparity. In particular, participants have conveyed concern that the environmental contaminant mercury could be causing gastric cancer.

Among the small participating communities, there were too few gastric cancer cases to investigate risk factors for cancer directly. Instead, intermediate endpoints provided a more efficient alternative; a widely accepted model of gastric carcinogenesis shows deleterious changes in the gastric mucosa are initiated by chronic gastritis, followed by gastric atrophy and intestinal metaplasia. This dissertation investigates the hypothesis that low doses of mercury ingested through fish and marine mammal consumption increases the risk of severe chronic gastritis, atrophy, and intestinal metaplasia among residents of Canadian Arctic communities.

Methods

Systematic literature review identified published articles presenting human tissue concentrations of mercury stratified by fish consumption frequency for meta-analyses that assessed sources of variation across studies in the relationship between mercury intake and mercury concentrations in hair. Two analyses were conducted: multivariate random-effects

meta-regression of summary data reported in the literature; multivariable random-effects regression of pooled raw data provided by authors of identified reports.

In fall 2016, a fish/whale-focused food-frequency questionnaire was administered to residents of participating communities. Hair samples were collected for biochemical measurement of methylmercury concentration. Methylmercury was measured in the full-length of each hair sample using gas chromatography inductively coupled plasma-mass spectrometry. Multivariable random-effects linear regression estimated beta-coefficients and 95% confidence intervals (CIs) for the effect of fish/whale consumption frequency on hair-methylmercury concentrations.

Pathological assessment was facilitated by endoscopy with gastric biopsy offered in Aklavik (2008) and Fort McPherson (2012), Northwest Territories and Old Crow (2011), Yukon. A pathologist graded the severity of gastric pathologies using the updated Sydney System. Multivariable logistic regression estimated log odds, odds ratios and 95%CIs for the effect of hair-methylmercury concentration on the prevalence of severe chronic gastritis, gastric atrophy, and intestinal metaplasia.

Results

The systematic review identified 87 eligible articles. The analysis of summary data showed that hair mercury concentrations increase with increasing fish consumption to a degree that varies greatly across studies. Specifically, while the direction of this relationship was consistent across studies, the strength of the trend varied. The magnitude of between-study variation was not reduced by adjustment for distributions of age or sex. Analysis of pooled datasets showed similar results, with a high degree of between-study variation for all exposure contrasts, after adjusting for age and sex.

In fall 2016, 101 participants provided hair samples and diet data. The mean number of different species eaten by participants was 3.50 (SD:1.90). The mean hair-methylmercury concentration was 0.60µg/g (SD:0.47). There was a positive association between consumption of fish and marine mammals in each season and hair-MeHg concentration, after adjusting for sex, hair length and use of permanent hair treatments.

Among 80 participants with complete data, the proportions with severe chronic gastritis, atrophy and intestinal metaplasia were 38%, 29% and 17%, respectively. The adjusted log odds of severe chronic gastritis and atrophy were highest among those with hair-methylmercury ≥1µg/g when estimated selenium intake was 0 µg/kg body weight/week. As estimated selenium intake increased, the adjusted log odds of each outcome approached 0 for all mercury exposure levels.

Conclusions

Meta-analysis of summary and pooled data demonstrated that accurate assessment of exposure to mercury through diet requires consideration of factors beyond age and sex. Among participants from Canadian Arctic communities, hair-methylmercury concentrations were below the 6.0µg/g threshold for safe exposure levels defined by Health Canada, suggesting that their fish/whale consumption practices are not placing them at elevated risk of known serious health outcomes associated with exposure. However, this research yielded evidence of a relationship between higher hair-methylmercury concentrations and increased odds of severe chronic gastritis and gastric atrophy, which may be mediated and modified by selenium intake.

Preface

This dissertation is original work completed by Emily V. Walker (EVW). This dissertation research received ethics approval from the University of Alberta Health Research Ethics Board, as a component of the project "Addressing Community Concerns about Risks from *H.pylori* Infection in the Circumpolar North"; Study ID: MS21_Pro00007868, Amendment ID: Pro00007868_AME17, approval date September 19, 2016. Fieldwork for this research was conducted in the Northwest Territories and Yukon, requiring two territorial research licenses. The Aurora Institute approved an amendment to license number 15785 to carry out this research on July 6, 2016. Yukon Tourism and Culture issued a "Scientist and Explorers License" for this research on October 12, 2016, license number: 16-78S&E.

Some of the research conducted as part of this dissertation was the result of collaborations. Collaborators are: Dr. Karen J. Goodman (KJG), Dr. Christian C. Abnet (CCA), Dr. Yan Yuan (YY) and Dr. Safwat Girgis (SG). Chapters 1 and 5 are the original unpublished work of EVW; conceptualized and written by EVW, with input from KJG, CCA, YY and SG. Chapters 2-4 contain the unpublished work of EVW, who conceptualized and wrote each paper with guidance from KJG and input from CCA, YY and SG.

Chapter 2 contains a systematic review and meta-analysis prepared for submission to a peer-reviewed journal for publication. EVW designed the review methods with guidance from KJG and input from CCA, including search strategy and inclusion/exclusion criteria. EVW conducted the search, reviewed the search results, identified articles that met inclusion/exclusion criteria, and extracted data from all selected articles. The article selection and data extraction processes were repeated by independent reviewers (two trainees: a medical student and a MSc-epidemiology student) who were supervised by EVW. EVW contacted the corresponding authors of all included articles to request de-identified raw data. EVW designed the statistical analysis plan and conducted the analyses with input from KJG and YY. EVW wrote the manuscript with input from KJG, CCA, YY and SG.

Chapter 3 contains original research by EVW prepared for submission to a peer-reviewed journal for publication. EVW designed this component of the research, with guidance from KJG and input from CCA, YY and SG. EVW designed the food-frequency questionnaires with input from KJG and local community representatives. EVW conducted the interviews and collected hair samples from 101 participants from arctic communities. The collected hair

samples were analyzed by the University of Alberta Biogeochemical Analytical Service Laboratory (BASL). EVW designed the statistical analysis plan and conducted the analyses with input from KJG and YY. EVW wrote the manuscript with input from KJG, CCA, YY and SG.

Chapter 4 contains original research by EVW prepared for submission to a peer-reviewed journal for publication. A research assistant helped collect additional food frequency data through telephone interviews. EVW designed the statistical analysis plan and completed the analysis with input from KJG, CCA and YY. EVW wrote the manuscript with input from KJG, CCA, YY and SG.

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I would also like to thank my supervisory committee members, Drs. Yan Yuan, Christian Abnet and Safwat Girgis, for their insight and constructive feedback. Each of you provided a unique and valuable perspective that challenged me to think in new ways and taught me a great deal.

This work would not have been possible without the hard work of the members of the CAN*Help* Working Group. I would like to specifically acknowledge some of my colleagues from this team, whom I have had the privilege of working with throughout my graduate studies: Hsiu-Ju Chang, Janis Geary, Amy Colquhoun, Laura McAlpine, Ali Assi and Katharine Fagan-Garcia – it has been wonderful working with all of you! I would also like to thank Megan Lukasewich, Miranda Wan, Taylor Cromarty and Bushra Alam for their help with data collection and reviewing articles.

Our team is fortunate to include several representatives from northern communities, who have been instrumental in the success of this research. My sincere thanks to Billy Archie, Gladys Edwards, Robert Buckle, Velma Illasiak, Bonnie Koe, Rachel Munday, Paul Josie, Kathie Nukon, Megan Williams, Winnie Greenland, Gina Neyando, Georgina Neyando and Liz Wright. I would also like to thank the community nurses and health center staff for their support.

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I am especially appreciative of my patient and supportive husband, Andrew. Andrew, you are constantly inspiring me with your work ethic and drive to reach your fullest potential. I have learned so much from you over the years and am so lucky to have you as a partner. This wouldn't have been possible without you.

And last but not least, I am thankful to my wonderful dog Sydney, for sleeping on my feet and keeping me company during the early mornings and late evenings working on this dissertation.

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List of Abbreviations

FFQ	Food-Frequency Questionnaire
FCF	Fish Consumption Frequency
Hg	Mercury
MeHg	Methylmercury
THg	Total mercury
CI	Confidence Interval
SD	Standard Deviation
SE	Standard Error
PUD	Peptic Ulcer Disease
UBT	Urea Breath Test
cagA	Cytotoxin-Associated Gene
vacA	Vacuolating Cytotoxin Gene
ROS	Reactive Oxygen Species
CS	Cross-Sectional
PC	Prospective Cohort
SCS	Series Cross-Sectional
CC	Case-Control
RC	Retrospective Cohort
CV-AAS	Cold Vapour Atomic Absorption Spectrometry
AAS	Atomic Absorption Spectrometry
AA	Atomic Absorption
CGA-AAS	Combustion Gold Amalgamation Atomic Absorption
GC	Gas Chromatography
HV-AFS	Hydride Vapour Atomic Fluorescence Spectrometry
TD-AAS	Thermal Decomposition Atomic Absorption Spectrophotometry
DMA	Direct Mercury Analyzer
GC-ICP-MS	Gas Chromatography Inductively Coupled Mass Spectrometry
ICP-MS	Inductively Coupled Mass Spectrometry
OC-GA	Oxygen Combustion Gold Amalgam
CV-AFS	Cold Vapour Atomic Fluorescence Spectrometry
GF-AAS	Graphite Furnace Atomic Fluorescence Spectrophotometry

Chapter 1: Introduction

While the incidence of gastric cancer has decreased in recent decades, it continues to present a substantial public health challenge in populations around the globe [1]. Gastric cancer is responsible for a large portion of the global cancer burden [1,2]. Recent reviews have shown it to be the 5th most common cancer and 2nd leading cause of cancer deaths worldwide [1,2]. However, evidence suggests that some populations are disproportionately affected by this disease relative to others [1,2]. In particular, Indigenous populations consistently experience a higher burden of gastric cancer relative to non-Indigenous populations residing in the same geographic areas [1]. This contrast is visible within Canada, where Indigenous populations residing in the western Canadian Arctic experience a disproportionate burden of gastric cancer and other digestive diseases, relative to multi-ethnic populations in southern regions [3–6]. Despite this, research investigating the factors associated with this disparity is relatively limited.

In a widely accepted model of gastric carcinogenesis, chronic gastritis is the first step in a cascade of deleterious pathological changes leading to gastric cancer [7–9]. Chronic gastritis is a pathological condition characterized by sustained presence of inflammatory markers in the gastric mucosa [7–10]. The next step in this pathway is gastric atrophy, characterized by depletion of gastric glands [7–10]. From gastric atrophy, lesions may progress to intestinal metaplasia, characterized by the replacement of depleted glands with phenotypically intestinal cells [7–10].

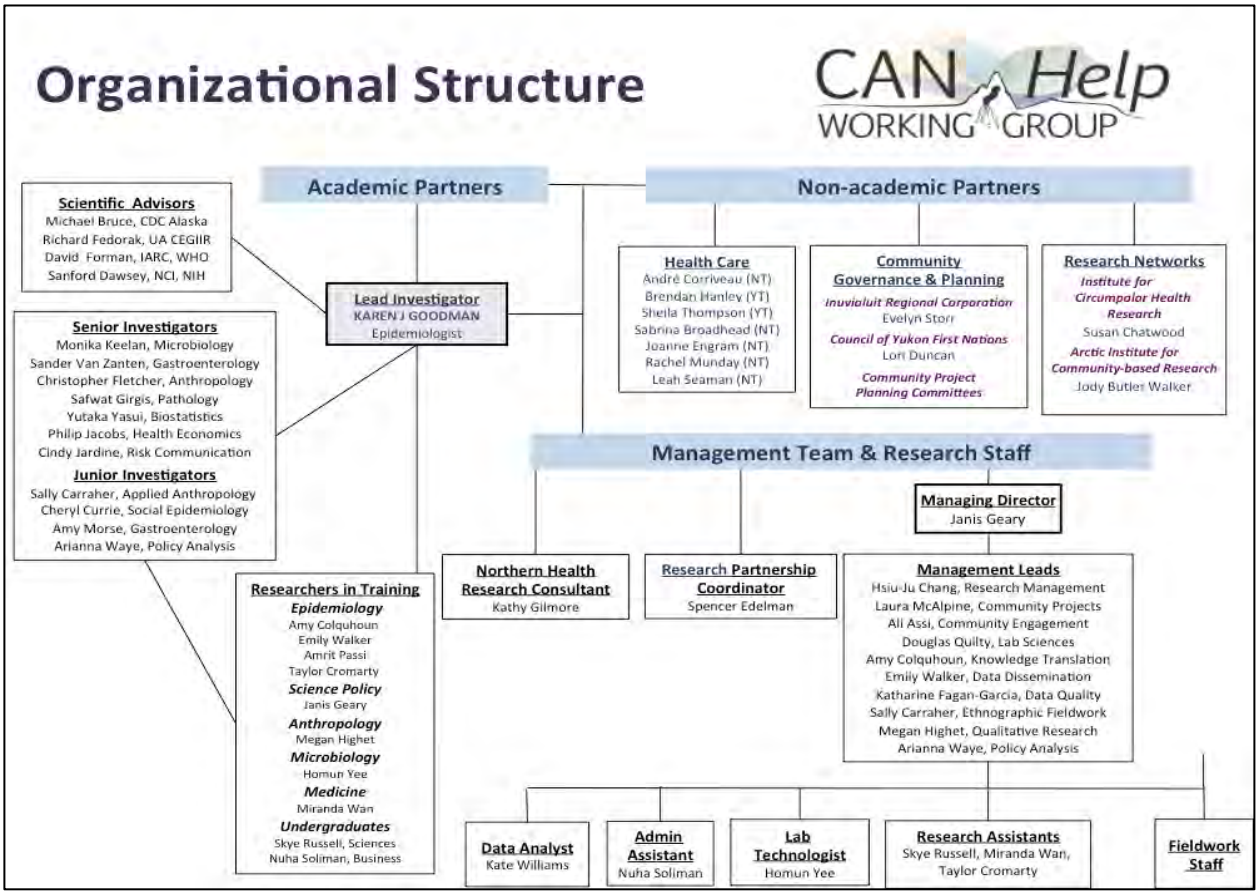
There are five broad categories of known causes of gastric mucosal injury that can lead to gastritis and more advanced gastric pathologies: biological agents; exogenous and endogenous chemicals; hypoxia and ischemia; physical factors; and genetic abnormalities [11–13]. The most common known cause is persistent infection with *Helicobacter pylori*, a gram-negative bacterium that infects the stomach and/or duodenum [11–13]. However, at each stage along the pathway of histopathological changes to the gastric mucosa, the risk of progression to more advanced lesions and ultimately gastric cancer is influenced by the interplay of several factors [14,15]. In general, factors hypothesized to play a role include: the prevalence of infection with *H.pylori* strains with factors that influence virulence; host susceptibility; diet and other exposures related to lifestyle; and environmental exposures [11–15]. However, the relative impact of each of these factors on the pathogenesis of gastric lesions and risk of gastric cancer is poorly characterized in the scientific literature [14,15].

The Canadian North Helicobacter pylori (CANHelp) Working Group

The research presented in this dissertation was conducted within ongoing community-driven projects led by the CAN*Help* Working Group in western Canadian Arctic communities. The CAN*Help* Working Group formed during 2006-2008 in response to concerns raised by community representatives about *H.pylori* infection and gastric cancer risk. The CAN*Help* research program is a collaborative effort, linking northern Canadian communities, their health care providers and regional health authorities with investigators from a variety of disciplines at the University of Alberta (figure 1). The CAN*Help* Working Group has three main objectives: 1. Obtain representative data from diverse settings in northern Canada for informing regional public health strategies for reducing risks from *H.pylori*; 2. Conduct policy analyses to identify cost-effective *H.pylori* management strategies that are ethically, economically and culturally appropriate for northern communities; 3. Develop knowledge exchange strategies that help community members understand *H.pylori* health risks as well as available solutions and challenges for reducing these risks.

In order to conduct a comprehensive investigation of *H.pylori* infection and associated disease in northern Indigenous populations, the CAN*Help* Working Group established projects in each community where residents sought participation. A planning committee made up of community representatives guided the conduct of each project. Each project planning committee elected to follow the same design as previous projects to enable valid comparisons across communities. Each project included five main components: non-invasive screening for *H.pylori* infection; questionnaire-based interviews on clinical history and socio-environmental characteristics of individuals and households; upper endoscopy with gastric biopsy for endoscopic, histopathological and microbiological examination; treatment to eliminate *H.pylori* infection; and knowledge exchange with stakeholders. Data collection at baseline permitted cross-sectional analysis and repeated data collection at later time points permitted follow-up analysis. Input from the local planning committees ensured that research activities were in keeping with community priorities and culturally appropriate.

Figure 1: *Organizational structure of the CANHelp Working Group, 2016*



Participating Communities

The first project launched in the hamlet of Aklavik, Northwest Territories (NT) (2006 census population=590) in 2007 [16,17]. This hamlet is located in the Mackenzie Delta at the confluence of the Peel and Mackenzie rivers, 113 km south of the Arctic Coast (Figure 2) [16–18]. Aklavik is a multi-ethnic community, with ~92% identifying as Gwich'in (Athabascan First Nation), Inuvialuit (Inuit) or Métis [16,17]. Residents continue to engage in traditional practices, including muskrat trapping and whaling [16,17]. Aklavik is accessible by water or air in the summer and ice road in the winter [19–21]. The second project began in 2010 in Old Crow, Yukon (YT) (2011 census population=245) [19,22]. Old Crow is the northernmost community in Yukon, situated on the Porcupine River (Figure 3) [19,22–24]. Approximately 85% of residents identify as Vuntut Gwich'in, which means "People of the Lakes" [19,22,23]. Their name is derived from the annual migration to Crow Flats, an area ~43 km north of Old Crow with numerous lakes [19,22,23]. Residents continue to rely on traditional practices such as trapping, hunting and fishing [19,22,23]. In particular, the Porcupine Caribou (*Rangifer tarandus granti*) herd

continues to serve as the primary source of food and raw materials for clothing and crafts [19,22,23]. Old Crow is accessible only by air year round [19–21]. The third project launched in Fort McPherson, NT (2011 census population=792) in 2012 [25]. Fort McPherson is situated on the banks of the Peel river (Figure 2) [18,25]. Residents of Fort McPherson predominantly identify as Tetlit Gwich'in (~90%) [25]. Many residents continue to follow a traditional lifestyle of hunting, trapping and fishing [19–21]. Fort McPherson is accessible by road with a ferry crossing in the summer and ice road in the winter [19–21]. While residents of the 3 communities maintain traditional cultural practices, their lifestyles incorporate modern technologies [19–21].

To assess the extent to which the subsets of each community that participated in CAN*Help* Working Group projects were representative of their respective communities, the distributions of key demographic characteristics among project participants and available census data were compared. This analysis demonstrated that the distribution of ethnicity (Indigenous versus non-Indigenous) was similar in the sample populations and the respective census populations [26]. However, individuals aged 0-19 years were underrepresented in the study population [26]. Additionally, study participants had a higher median income than reported for each census population [26].

Development of the Research Aims

Exposure to exogenous chemicals is a major concern in participating communities, as residents are aware of the vulnerability of Arctic ecosystems to contaminants. In keeping with the community-driven approach of the CAN*Help* Working Group, which uses community input to guide the research, I used qualitative inquiry to identify specific research questions relating to gastric health that address community concerns about environmental contaminants. I received training in qualitative research methods from anthropologist Sally Carraher, PhD, the CAN*Help* Working Group Ethnographic Fieldwork Lead. The method I followed was Qualitative Description, which aims to generate a thorough description and summary of the phenomenon of interest [27], using community informants as data sources. The interview instrument I developed for this purpose was semi-structured in design, with 8 open-ended questions prompting participants to provide comprehensive descriptions of: what community members mean when they use the words "contaminant" or "toxin"; the level of concern in their community around environmental contaminants; whether there are specific contaminants that are considered most concerning, and if so which ones; and the health effects that residents are most worried about. I used purposive sampling, a non-probability based method, to select individuals for participation [28]. As the goal was to characterize the shared concerns of community members, recruitment targeted key

informants from each community. I defined "key informant" as a resident likely to have a high level of insight into community concerns. I continued to select individuals from each community until saturation was achieved, with saturation defined as the point at which responses no longer added new information [29]. I used content analysis to identify patterns or themes across responses that contribute to a comprehensive understanding of shared perceptions and concerns [27].

I completed a total of 12 interviews with key informants from all participating communities. Most respondents expressed concern about environmental contaminants, particularly mercury, affecting digestive health and causing cancer. Participants indicated that since residents of Arctic communities continue to follow a subsistence lifestyle, they see themselves as uniquely vulnerable to contamination of local water sources and aquatic or terrestrial animals, on which they rely as part of a traditional diet. Their comments suggest that their strong dependence on the natural environment coupled with the perception that they are unable to effectively intervene on processes leading to the release of pollutants in order to protect their ecosystem has led to a high level of anxiety.

Review of the literature on mercury contamination in the Arctic, mercury toxicity and mechanisms of gastric mucosal injury, indicates that community concerns are warranted [11,30–35]. However, while the potential for environmental exposures to contribute to the pathogenesis of gastric disease has been acknowledged in the scientific community, epidemiological investigation of the effect of chronic exposure to specific contaminants like mercury on gastric disease is lacking. The gap in the scientific literature provided a compelling rationale for investigation of this environmental health concern through research conducted in partnership with northern Indigenous communities.

Figure 2: *Map of the Northwest Territories, Canada, showing the location of Aklavik and Fort McPherson*

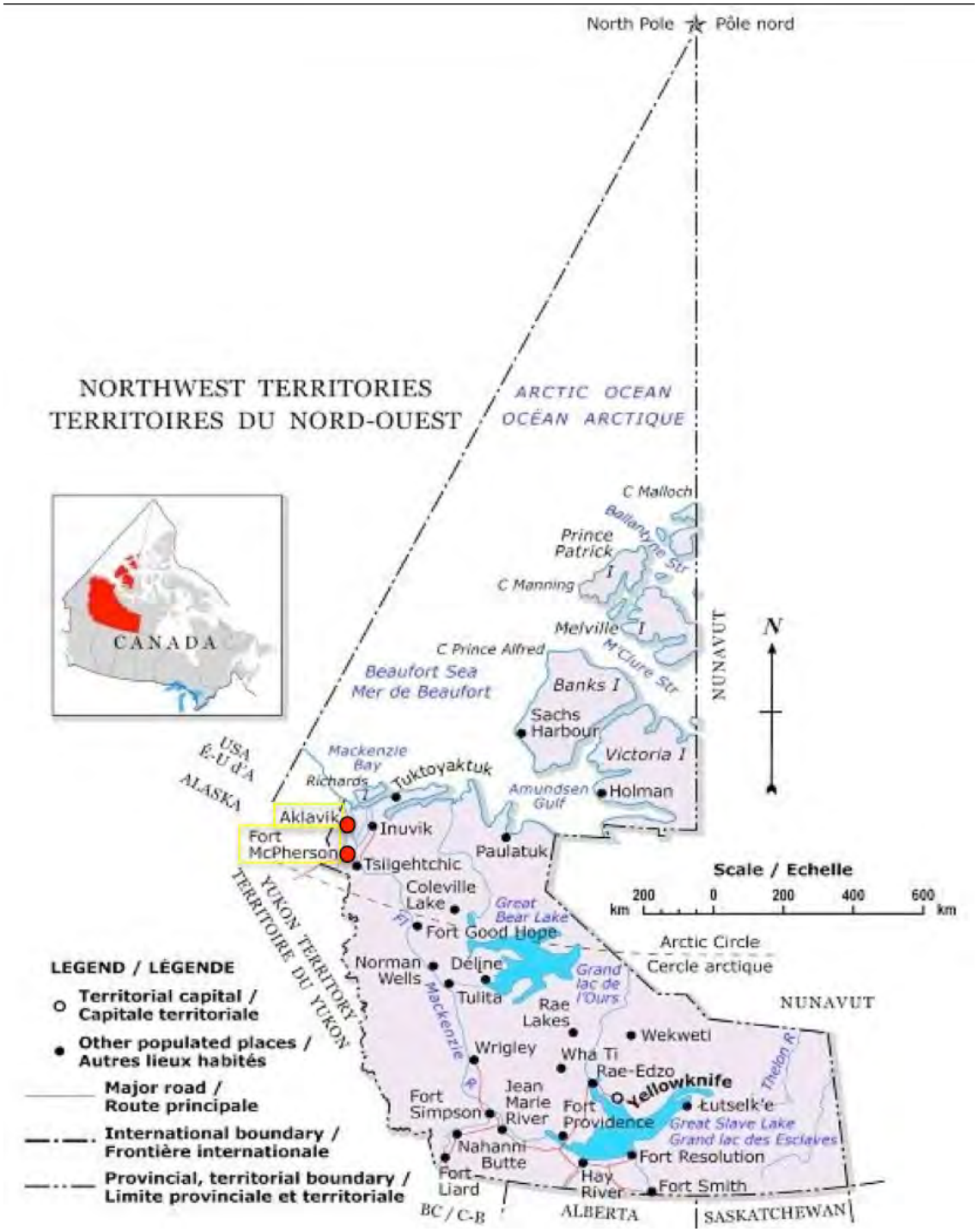


Figure 3: *Map of Yukon, Canada, showing the location of Old Crow*

Research Aims

Since the communities participating in this research are small, the number of gastric cancer cases was not high enough to permit investigation of factors associated with risk of developing gastric cancer directly. However, the widely accepted model of gastric carcinogenesis identifies the progression from chronic gastritis to more advanced gastric pathologies as the initial part of the pathway to gastric cancer, based on evidence of its strong association with gastric cancer risk; thus, chronic gastritis, gastric atrophy and intestinal metaplasia are considered intermediate endpoints that can improve the efficiency of studies aiming to investigate factors associated with gastric cancer risk [14]. Therefore, this

research investigates the hypothesis that chronic ingestion of low doses of mercury through fish consumption increases the risk of severe chronic gastritis, gastric atrophy, and intestinal metaplasia, among residents of Canadian Arctic communities. Specifically, this research aims to:

1. Conduct a systematic review and meta-analysis in order to:
    a. Identify and summarize the published literature pertaining to human tissue concentrations of mercury and consumption of fish or seafood;
    b. Assess the presence and shape of the dose-response relationship between intake and internal dose across populations represented in the literature; and
    c. Quantify the extent to which various population characteristics explain any variation in this relationship across populations;
2. Characterize dietary intake of fish, fish products and marine mammals and concurrently collect hair samples for biochemical measurement of hair mercury level among participants of CAN*Help* Working Group projects; and
3. Develop a statistical model to predict hair mercury levels among individuals who did not provide hair samples for biochemical measurement of mercury level, but provided data on consumption of fish or marine mammals and provided gastric biopsies for histopathological evaluation;
4. Estimate the effect of measured or predicted hair mercury level on each of three gastric disease outcomes (severe gastritis, gastric atrophy, intestinal metaplasia) among CAN*Help* Working Group project participants with pathologically evaluated gastric biopsies.

Background

Chronic Gastritis

Chronic gastritis is characterized by a higher density of mononuclear inflammatory cells in the gastric mucosa than typical [7–10]. Specifically, infiltration of the gastric mucosa with the following cell types is considered characteristic of chronic gastritis: lymphocytes, plasma cells, eosinophils and mast cells [7–10]. Inflammation of the gastric mucosa ranges in severity, which is graded according to the density of inflammatory markers [7–10]. The determinants of gastritis severity are not well understood. Among participants of CAN*Help* Working Group community projects in Aklavik NT, Fort McPherson NT, and Old Crow YT with biopsies evaluated during 2008-2013, the prevalence of chronic gastritis was 75% (234/310). Among

those with chronic gastritis, 12% (28/234) were graded mild, 42% (99/234) were graded moderate, and 46% (107/234) were graded severe. *H.pylori*-positivity was assessed using three methods: non-invasive screening with the urea-breath test (UBT); histopathology; and culture. The *H.pylori* infection status for each participant was classified using all available information. An algorithm was used to classify the infection status of participants with discordant results. The prevalence of *H.pylori*-infection among all participants with biopsies evaluated was 78% (243/310). The prevalence of *H.pylori*-infection among individuals with chronic gastritis was 95% (222/234). The prevalence of chronic gastritis among participants with *H. pylori* infection was 91% (222/243). Placing these frequencies into a broader context is complicated by limited evidence on the occurrence and severity of chronic gastritis from population-based studies in the published literature [36]. In one community-based screening program in Taiwan, 325 individuals identified through a population list recruited between 1995 and 1999 underwent endoscopic examination with gastric biopsy [37]. In this population, the prevalence of histopathologically graded non-atrophic gastritis was 46% (148/325) [37]. However, the authors did not differentiate between acute and chronic gastritis and the distribution of gastritis severity and prevalence of *H.pylori* infection was not reported [37].

Most of what is known about the distribution of chronic gastritis has been generated in studies for which participants were recruited from hospitals or clinics where they were undergoing upper endoscopy as part of diagnostic evaluation [36]. Comparison to other populations represented in the available literature indicates that the frequency of severe chronic gastritis among the CAN*Help* Working Group projects is higher than expected, even for those with *H.pylori*-infection [36]. For example, among 401 *H.pylori*-positive patients with biopsies evaluated at the University of Alberta Hospital in Edmonton, Alberta, Canada, the prevalence of chronic gastritis of any severity was 99% (95%CI: 97%, 100%; 397/401) (compared to 91% (95%CI: 87%, 95%; 222/243) among participants from Aklavik, Fort McPherson and Old Crow with gastric biopsies evaluated) [36]. However, in this multi-ethnic southern Canadian population, among 282 individuals with histopathologically graded chronic gastritis, 40% were graded mild, 55% were graded moderate and 5% were graded severe [36]. In a multi-center study of 1123 individuals attending endoscopy clinics across Europe for a variety of conditions, the prevalence of histopathologically diagnosed chronic gastritis was 57% (639/1123) [38]. In this European population, the prevalence of *H.pylori* infection was 19% (210/1123) [38]; data on the distribution of gastritis severity were not presented [38]. Among 94 patients seeking care for gastrointestinal symptoms at a hospital in Pakistan, the prevalence of histopathologically graded chronic gastritis was 95% (89/94) [39],

with 59% graded mild, 43% graded moderate, and 4% graded severe [39]. The prevalence of histopathologically diagnosed *H.pylori* infection was 88% in this Pakistani patient population [39]. Therefore, overall, the available evidence shows that nearly all *H.pylori*-positive populations have chronic gastritis, however there are few reports that show the distribution of chronic gastritis severity. The few reports that do include the distribution of chronic gastritis severity show a much lower prevalence of severe gastritis among *H.pylori*-positive people than observed among participants of CAN*Help* Working Group community projects.

Gastric Atrophy

Following chronic gastritis, the next step in the progression toward more serious disease is gastric atrophy, characterized by depletion of gastric glands [7–10]. Following the loss of gastric glands, the mucosa may regenerate and revert to its normal functional form, or undergo adaptive changes resulting in the replacement of the former structures with other tissue types [7–10]. In the absence of regeneration, the stromal space formerly containing gastric glands becomes filled with fibroblasts and extracellular matrix [7–10]. Evidence suggests that among individuals with *H.pylori*-infection, the proportion that progresses from chronic gastritis to atrophy varies across populations [14]. Gastric atrophy is rarely observed among individuals younger than 30 years in western populations [14].

Among 310 individuals with biopsies evaluated between 2008 and 2013 from Aklavik, Fort McPherson and Old Crow, the prevalence of gastric atrophy was 31%. Among participants with gastric atrophy, the distribution of severity was 71% (67/95) mild; 25% (24/95) moderate, and 4% (4/95) severe. Of 76 individuals under 30 years of age, the prevalence of gastric atrophy was 28%. The prevalence of *H.pylori* infection among participants with gastric atrophy was 99% (94/95). Data on the frequency of progression to atrophic gastritis in population-based studies is limited [14,40]. Evidence on the distribution of gastric atrophy has been generated predominantly by clinic-based studies of patients diagnosed with *H.pylori* infection or other gastrointestinal diseases [36,40]. Overall, the frequency of gastric atrophy among participants of CAN*Help* Working Group projects with biopsies evaluated was not consistently higher or lower than that of other populations represented in the reviewed literature [36,39,41].

In the Taiwanese community-based screening program, the prevalence of atrophy was 13% (42/325) [37]. When compared to the multi-ethnic southern urban population in Canada, the prevalence of gastric atrophy among project participants was substantially higher [36]: among

the *H.pylori*-positive University of Alberta Hospital patients with biopsies evaluated, the prevalence of gastric atrophy was 2.2% (9/401) [36]. Conversely, the frequency of atrophy among CAN*Help* Working Group project participants was much lower than that of the 94 Pakistani hospital patients, of whom 70% had histopathologically diagnosed gastric atrophy [39]. However, among those diagnosed with atrophy, the distribution of severity was similar to that of the CAN*Help* Working Group project participants: of 66 Pakistani patients diagnosed with atrophy, 70% (46/66) were graded mild, 23% (15/66) were graded moderate, and 8% (5/66) were graded severe [39]. Finally, the frequency of atrophy and distribution of severity among CAN*Help* Working Group project participants was similar to that of the patients in the multi-center Chinese study: Among 8,892 patients, the prevalence of histopathologically diagnosed gastric atrophy was 26% [41]; of those diagnosed with atrophy, 65% (1,486/2,291) were graded mild, 28% (647/2,291) were graded moderate, and 7% (158/2291) were graded severe [41].

Intestinal Metaplasia

Following depletion of gastric glands, atrophic lesions may progress to intestinal metaplasia, which is characterized by the replacement of depleted gastric glands with small intestinal cells, such as goblet cells and enterocytes [7–10]. Intestinal metaplasia can be divided into two types: type 1 is characterized by the presence of normal intestinal epithelium; type 2, or incomplete metaplasia, is characterized by a disorganized combination of irregular goblet cells and immature mucinous cells [10]. Risk of progression to gastric cancer is thought to be higher in the presence of incomplete metaplasia [10]. As with gastric atrophy, intestinal metaplasia is rarely observed in individuals younger than 30 years in western populations [14].

Of 310 participants from Aklavik, Fort McPherson and Old Crow with biopsies evaluated between 2008 and 2013, the prevalence of intestinal metaplasia was 14%. Among those with intestinal metaplasia, 65% (28/43) were graded mild, 28% (12/43) were graded moderate and 7% (3/43) were graded severe. The prevalence of *H.pylori* infection among participants with intestinal metaplasia was 88% (38/43). Of 78 participants under 30 years of age, the prevalence of intestinal metaplasia was 3%. Valid comparison of the frequency and severity of intestinal metaplasia among participants of CAN*Help* Working Group projects with that of populations represented in the published literature is hampered by the predominance of study populations recruited from hospitals or clinics, which may not have a similar distribution of intestinal metaplasia as the broader source population [36]. However,

review of the available literature does not yield evidence of a greater-than-expected frequency of intestinal metaplasia among CAN*Help* Working Group project participants [36].

In the Taiwanese community-based screening program, the prevalence of intestinal metaplasia was 36% (117/325) [37]. Among the *H.pylori*-positive University of Alberta Hospital patients with gastric biopsies evaluated, the prevalence of intestinal metaplasia was 15% (60/401) [36]. The prevalence of intestinal metaplasia among the 8,892 patients in the multi-center Chinese study was 24% [41], of whom 69% (1,451/2,095) were graded mild, 24% (504/2,095) were graded moderate, and 7% (140/2,095) were graded severe [41]. The prevalence of intestinal metaplasia among the 94 Pakistani hospital patients was 4% [39]. Of 4 individuals with intestinal metaplasia, 25% (1/4) were graded mild and 75% (3/4) were graded moderate [39].

Gastric Ulcers vs. Duodenal Ulcers

Chronic gastritis is also known to play a role in initiating the pathogenesis of peptic ulcer disease (PUD) [7,8]. Evidence has shown that the anatomical location of an ulcer is indicative of whether the affected individual is at increased risk of more advanced gastric disease, and, in particular, that ulcers in the duodenum do not usually occur with changes in the gastric mucosa that are likely to progress to gastric cancer [42]. Conversely, ulcers in the stomach (referred to as gastric ulcers) more frequently occur with changes in the gastric mucosa on the pathway towards gastric cancer [42]. At the population level, the ratio of gastric to duodenal ulcers can be interpreted as an indication of gastric cancer risk among those with *H.pylori* infection or associated gastric pathologies, given evidence that gastric cancer rates are high in populations where the gastric to duodenal ulcer ratio is greater than one and low where this ratio is less than one, as well as evidence that individuals with gastric ulcers have an increased risk of gastric cancer, whereas the risk is decreased in those with duodenal ulcers [43,44]. The endoscopic findings from CAN*Help* Working Group projects show the frequency of gastric ulcers is 3 times that of duodenal ulcers: Among 311 individuals with data on endoscopic findings from Aklavik, Fort McPherson and Old Crow, 9 had gastric ulcers and 3 had duodenal ulcers. These findings from CAN*Help* Working Group projects indicate that the participating communities have an elevated risk of gastric cancer [42].

H.pylori Infection

The most common known cause of the chronic gastritis that leads to gastric mucosal injury and more advanced gastric pathologies is chronic *H.pylori* infection [11,45,46]. This bacterial infection is found in populations around the globe; however, some populations experience a disproportionate burden from *H.pylori* infection and associated disease relative to others [47–50]. The only known source of *H.pylori* bacteria is the human stomach [51]. *H.pylori* infection is transmitted from person to person through contact with infected digestive fluids [51]. The predominantly hypothesized transmission pathways are gastro-oral, fecal-oral and oral-oral; however, little evidence differentiates the relative importance of each pathway [51]. Compelling evidence suggests that transmission occurs most readily during bouts of acute gastroenteritis with vomiting and diarrhea [52,53]. Evidence on extra-gastric sources of *H.pylori* and the potential for the bacteria to be transmitted through other pathways has been inconclusive [54]. Evidence suggests that *H.pylori* infection is most often acquired during childhood and can persist in the absence of treatment [55]. However, infection onset is not marked by specific symptoms, most persistent infections are asymptomatic, and *H. pylori* antibodies often reduce to undetectable levels following elimination of the infection [55]. Because of this, accurate estimation of the incidence of acquisition or spontaneous elimination is not practical using currently available detection methods.

Data from major urban centers across Canada show the prevalence of *H.pylori* infection is relatively low, with higher prevalence among older individuals [3,56–58]. In a prevalence study conducted in the province of Manitoba in 1997, prevalence of *H.pylori*-infection among 469 individuals aged 20-34 years was 35% [58]. In the same study, the prevalence of *H.pylori*-infection among 265 individuals aged 35-65 years was 46% [58]. In a prevalence study published in 2003 of 1013 patients with uninvestigated dyspepsia aged 18 to 86 years from 49 physician clinics in 6 Canadian provinces, 30% were infected with *H.pylori* [56]. In another prevalence study published in 2005 of 309 patients aged 18-83 years with uninvestigated heartburn-dominant dyspepsia from 46 physician clinics across Canada, 31% were infected with *H.pylori* [57]. Lower prevalence in pediatric populations has been shown in a 2005 study of 246 pediatric endoscopy patients aged 5 to 18 years from four academic centers, with a prevalence of 5% [3]. Since evidence suggests that *H.pylori* infection is most readily acquired during childhood, the low prevalence in children relative to adults indicates a secular trend towards decreasing transmission, with more frequent transmission in earlier eras and a reduction in transmission in major urban centers in recent years [3,58]. However, residents of western Arctic communities are disproportionately affected by *H.pylori* and associated

disease, relative to multi-ethnic populations in southern regions [3–6]. Community projects in Aklavik, Fort McPherson, and Old Crow, have revealed a high prevalence of *H.pylori* infection, with estimates ranging from 58-68% based on UBT screening.

Evidence suggests that some strains of *H.pylori* have a greater capacity to produce more severe gastric disease relative to others, determined by the presence of specific genes and allelic combinations [59]. The two genes considered most indicative of *H.pylori* virulence are the cytotoxin-associated gene (*cagA*), and the vacuolating cytotoxin gene (*vacA*) [59]. The *vacA* gene consists of 3 regions: signal (alleles s1 or s2); intermediate (alleles i1 or i2); and mid (alleles m1 or m2) [59]. The cytotoxic activity associated with the *vacA* gene varies across different combinations of alleles in the 3 regions [59]. Evidence suggests that strains of *H.pylori* with the s1 allele in the signal region, the i1 allele in the intermediate region, or the m1 allele in the mid region are more virulent than other strains [59,60]. In particular, *vacA* allelic combinations s1/m1 and s1/m1/i1 are thought to be associated with an increased risk of gastric cancer, compared to strains with *vacA* s2/m2 or *vacA* s2/m2/i2 [59,60].

The high burden of *H.pylori*-associated disease in Canadian Arctic populations relative to the Edmonton population and others represented in the published literature may be due in part to variation in frequencies of infection with *H.pylori* strains with different virulence factors. A total of 200 *H.pylori*-positive participants from Aklavik, Fort McPherson and Old Crow had microbiology data . Among these individuals, the prevalence of each virulence factor was: 49% *cagA* positive; 42% with *vacA* s1/m1; and 34% with *vacA* s1/m1/i1. The distribution of *H.pylori* strains with each of these virulence factors across categories of severity for each gastric pathology is shown in table 1. These findings show an increasing prevalence of each virulence factor with increasing severity of gastric atrophy, and an increased prevalence of each virulence factor among participants with severe chronic gastritis relative to others [61]. There was no evidence of a trend of increasing prevalence of any *H.pylori* virulence factor and increasing severity of intestinal metaplasia; however, the small number of participants with intestinal metaplasia graded as moderate or severe limit the statistical power for detecting a trend [61].

Table 1: *The prevalence of virulence factors within categories of severity for each gastric pathology among 200 individuals with microbiology data from Aklavik, Fort McPherson and Old Crow (2008-2012)*

	cagA (+)			*vacA* s1/m1			*vacA* s1/m1/i1		
	n	**%**	**p for trend**	**n**	**%**	**p for trend**	**n**	**%**	**p for trend**
Chronic Gastritis									
None	6	32		6	32		4	21	
Mild	4	40		4	40		4	40	
Moderate	32	42		25	32		20	26	
Severe	55	56	0.01	48	51	0.05	40	43	0.05
Gastric Atrophy									
None	43	37		37	32		29	25	
Mild	32	54		26	44		21	36	
Moderate	19	83		17	74		15	65	
Severe	3	100	<0.01	3	100	<0.01	3	100	<0.01
Intestinal Metaplasia									
None	75	45		66	39		53	32	
Mild	14	78		12	67		12	67	
Moderate	7	64		4	36		2	18	
Severe	1	33	0.10	1	33	0.54	1	33	0.57

Contamination of Arctic Ecosystems with Mercury Compounds

Environmental assessments of mercury levels in the circumpolar north substantiate community concerns about an increasing abundance of this heavy metal in Arctic ecosystems [33,62]. While mercury exists in the environment as a result of natural processes, evidence suggests that the concentration of mercury is increasing due to anthropogenic activities [33,62]. Anthropogenic emissions may contain mercury and thus directly contribute to mercury contamination [33,62]. Mercury emissions around the globe may become deposited in Arctic ecosystems due to the direction of atmospheric, oceanic and river currents facilitating long-range transport to the poles [33,62]. Further, anthropogenic emissions other than mercury are known to contribute to climate change [33,62]. The environmental impact of global climate change includes degradation of Arctic permafrost and changes to the organic carbon cycle, processes thought to result in increased levels of mercury in Arctic ecosystems [33,62].

Mercury Toxicity and Gastric Mucosal Injury

Of forms of mercury, methylmercury (MeHg), formed through methylation of divalent mercury by aquatic organisms, is thought to pose the greatest risk to human health [32,33,63–65]. This is due to its ability to bioaccumulate in aquatic food chains, and subsequent potential for human exposure through ingestion of contaminated fish or marine mammals [63,64,66–71]. Mercury-induced toxicity does not result from action on a single cellular target, and can lead to a wide range of toxic effects on tissues throughout the body [63,64,66–69,71,72]. The highly

reactive nature of MeHg results in a series of complex effects that initiate processes eventually leading to apoptosis [63,64,66–69,71,72]. Potential mechanisms through which mercury can induce damage to cells, genes and tissues include: interruption of intracellular calcium homeostasis [64,69,73,74]; oxidative stress [63,64,66,67,69,71,75,76]; alteration of glutamate homeostasis [63,69,76]; disruption of membrane potential [64]; alteration of protein synthesis [64,66]; disruption of excitatory pathways of the central nervous system [71,73–77]; and inhibition of protein synthesis [64,71]. Oxidative stress is considered one of the most common pathways through which mercury-induced cytotoxicity occurs [63,64,66,67,69,71,75,76]. Mercury-induced oxidative stress is characterized by modifications to DNA bases [66], mitochondrial damage [63,64,74] and lipid peroxidation [63,64,69,71,76,77]. The production of hydroxyl radicals exacerbates an imbalance in the ratio of reactive oxygen species (ROS) to antioxidants by depleting glutathione and selenium stores and inhibiting glutathione synthetase [66].

Review of the available scientific literature suggests regular exposure to methylmercury may directly lead to chronic gastritis and subsequent serious digestive disease through oxidative stress [11,30,31,78]. Proposed pathways through which ROS contribute to gastric mucosal injury include membrane damage through lipid peroxidation, protein dysfunction resulting from protein oxidation and disruption of DNA repair resulting from the oxidization of nucleic acids [30,31]. Interruption of repair mechanisms may result in apoptosis or mutagenic changes [30,31]. Therefore, while direct assessment of the potential for mercury to induce gastric mucosal injury has not been a focus of the scientific studies on mercury toxicity, review of the toxicokinetic and toxicodynamic properties of methylmercury and the mechanisms through which gastric cells become injured suggests it is reasonable to infer mercury could play a role in the pathogenesis of gastritis among individuals who consume large quantities of fish containing mercury concentrated in tissues.

Overview of Thesis Chapters

Findings from this research are summarized in three papers, which describe distinct components relating to the overall aims. The first paper (Chapter 2) contains a comprehensive systematic review and meta-analysis of the published literature pertaining to mercury exposure through fish consumption among populations around the globe. The main objective of this paper was to assess the extent to which population characteristics influence the relationship between fish intake and internal dose of mercury, as measured in biological media. Meta-analysis was used to quantify the degree of between-population variation in internal dose and to assess whether this variation is greater than would be expected based

on fish consumption patterns, along with the distribution of sex and age. Since ascertaining mercury exposure was not within the originally defined scope of the CAN*Help* Working Group community projects, the systematic review and meta-analysis contributed to the stated aims of this dissertation by guiding the methods used and the interpretation of measured tissue concentrations.

The second paper (Chapter 3) summarizes the exposure assessment component of this research. Specifically, this paper describes participants from Aklavik, Fort McPherson and Old Crow with respect to dietary intake of fish and marine mammals, dietary intake of other food items potentially related to mercury toxicokinetics, and biochemical measurements of methylmercury concentrations in hair samples. A total of 101 participants provided food frequency data and hair samples for laboratory measurement of methylmercury concentration. Multivariable logistic regression was used to estimate associations with hair-mercury level of fish and marine mammal consumption frequency and other exposures. Results from this component were used to ascertain exposure status for analyses aimed at estimating the effect of methylmercury exposure on gastric health outcomes. The third and final paper (Chapter 4) summarizes the statistical analyses aimed at estimating the effect of methylmercury exposure on each of the following outcomes: severe chronic gastritis, gastric atrophy and intestinal metaplasia. A total of 80 participants from Aklavik, Fort McPherson and Old Crow had data on methylmercury exposure through fish and marine mammal consumption and provided gastric biopsies for histopathological evaluation. Conclusions emerging from this thesis research are synthesized in Chapter 5.

Chapter 2: Systematic Review of the Literature on Fish Consumption and Human Tissue Concentrations of Mercury: Using Meta-Analysis to Investigate Heterogeneity across Populations Worldwide

Introduction

Mercury is a chemical element classified as a transition metal, which exists in the environment naturally as well as through anthropogenic processes [63,66,68]. Mercury has three valence states, elemental mercury (Hg^0), divalent inorganic mercury compounds (Hg^{2+}), and organic complexes [63,66,68]. Each state has its own toxicological profile and exhibits distinctive behaviour in environmental media [63,65–68,79]. Of organic mercury compounds, methylmercury (MeHg), formed through methylation of divalent mercury by aquatic organisms, is thought to pose the greatest risk to human health [32,33,63–65]. The elevated health risks posed by MeHg are due to its ability to accumulate in aquatic food chains, and its subsequent potential for human exposure through ingestion of contaminated fish or marine mammals [63,64,66–70,79]. Evidence suggests that one of the most important pathways for human exposure to mercury is consumption of fish, fish products and marine mammals that are likely to be contaminated with high concentrations of MeHg [63,64,66–70,79].

Due to its chemical properties, MeHg is considered the form of mercury with the greatest potential to affect human health [63,66–68,71]. MeHg is characterized by a high capacity to dissolve in fats (referred to as high lipophilicity), allowing it to readily absorb into the blood through the gastrointestinal tract and become widely distributed throughout the body, and is highly toxic to humans [63,64,66,67,69,71]. The most potent health effects associated with mercury exposure include functional impairment of the nervous system, renal failure and interruption of normal fetal development, all of which can be fatal [63,66–68,71]. More recently, studies have suggested an association between mercury exposure and cardiovascular disease [69]. In 1993, the International Agency for Research on Cancer classified mercury and mercury compounds as a possible human carcinogen [80]. Further, the body of evidence on serious health effects from mercury exposure has prompted the World Health Organization (WHO) to include mercury in a list of the 10 chemicals that present the greatest public health concern [81]. For this reason, WHO calls for enhanced monitoring of mercury exposure and widespread communication of risks associated with exposure among subsets of the population at increased risk of health effects [81].

In the context of exposure assessment, biological markers or biomarkers, can be defined as measurable indicators of biological changes occurring in response to the presence of foreign chemicals [82,83]. Biomarkers may be the chemical of interest itself, or metabolites or by-products produced in response to exposure [82,83]. Biomonitoring involves quantifying the concentration of biomarkers in biological media, such as bodily tissues or products [82,84,85]. There are several important advantages to using biomarkers to ascertain exposure levels [82,84,85]. Most notably, biomonitoring is considered the optimal approach for measuring exposure status in studies that aim to investigate associated health effects [82,85]. The superior suitability of this approach is because biomonitoring directly measures the internal dose of foreign chemicals of interest and accounts for inter-individual variation in rates of metabolism and excretion [82,85].

Methods other than biomonitoring for classifying human exposure to chemical elements use external measurements of chemicals in an individual's environment to estimate the internal dose [82,84,85]. The predominant limitation of such approaches is that assessments of chemical concentrations in the ambient environment are not reliably correlated with internal doses, due to several mediating factors, including: genotype; dietary patterns; body size and composition; health status; lifestyle habits and behaviours [28,82,84–86]. Despite this, environmental risk assessments often employ calculations intended to predict an individual's mercury intake, which is then used as a proxy for the internal dose [69,87]. A commonly used approach in human studies of mercury concentration resulting from fish consumption is to multiply species-specific fish muscle intake by the species-specific average mercury concentration and divide the product by an individual's body weight [69,87]. When individual anthropometric data are not available, average weights for different strata of age and sex are used to estimate exposure distributions in a population [87]. These approaches are more practical when there are insufficient resources for measuring biomarker concentrations, or participants willing to undergo potentially invasive sampling procedures [82,84,85]. However, stratification by age and sex may not adequately account for inter-individual variation in biological response to ingestion of mercury from fish, and may contribute to inaccurate estimation of internal dose [82].

The objective of this systematic review and meta-analysis is to assess the extent to which population characteristics influence the relationship between fish intake and the internal dose of mercury as measured in biological media. It aims, in particular, to assess whether

stratification of intake estimates by sex and broad categories of age adequately accounts for variation in individual responses to mercury exposure that, in turn, may lead to variation in internal dose beyond what would be expected based on fish consumption patterns.

Methods

PhD candidate EVW designed the review methods in accordance with optimal approaches for systematic reviews and meta-analyses, as described by Cochrane and by Greenland's chapter on meta-analysis in Modern Epidemiology, 3rd Edition [86,88]. She developed strict *a priori* inclusion and exclusion criteria for article selection to ensure that the results of the search were reproducible and the assessment of each article's eligibility for inclusion was systematic. This systematic review and meta-analysis adheres to the reporting guidelines outlined in the Meta-analysis of Observational Studies in Epidemiology (MOOSE) consensus statement [89].

Article Identification Protocol

EVW conducted a scoping review to guide the development of a comprehensive search strategy [90]. The scoping review collected MeSH terms and keywords from articles containing the desired information and examined the search strategies used in published systematic reviews with similar focuses to identify key databases and record any additional relevant MeSH terms. To capture all relevant publications, the comprehensive search reviewed multiple databases, including Embase®, Scopus®, Web of Science©, Medline®, PubMed® and LILACs©, using the search terms ("Seafood" OR "Mollusca" OR "Shellfish" OR "Fish" OR "Fishes") AND ("Mercury" OR "Methylmercury" OR "Methylmercury Compounds") AND ("Biological Markers" OR "Biomarkers/Analysis" OR "Hair/Analysis") AND ("Humans") to find entries indexed through April 2016. EVW examined the comprehensive review results to ensure that the search terms captured papers identified in the scoping review. She added search results from each database to a single folder in the reference manager Zotero (https://www.zotero.org/) and removed all duplicate entries. Additionally, following article selection procedures, she inspected reference lists from articles selected for inclusion for relevant articles that were not identified through the database searches.

Article Selection Protocol

The selection process consisted of two stages: first, reviewers screened the titles and abstracts for the following inclusion criteria: the title/abstract appears in English; the abstract summarizes findings from original research; and the title/abstract mentions

investigation of the association between diet and mercury exposure, as measured through biological markers. Second, articles selected during the first stage underwent full text review to see if they met additional inclusion criteria: the full text was written in English and the authors presented estimates of mercury concentrations in biomarkers across categories of fish consumption, defined either by the frequency, amount or type of fish meals consumed. The full review excluded articles if these data were only presented in figures lacking sufficiently detailed scales, as required for accurate recording of results, or if the results were limited to beta-coefficients from models that assume linearity since a goal of the meta-analysis was to assess the shape of the relationship between fish consumption frequency and biomarker concentrations of mercury [91]. The full review also excluded articles if they had any of the following characteristics: it summarized the findings of case-studies; the goal of the research was to measure the impact of interventions designed to mitigate exposure to mercury; or the study population was occupationally exposed to mercury. Both stages of the article selection process were carried out by two independent reviewers; once by EVW and once by one of two trainees (a medical student and an MSc-epidemiology student) supervised by EVW. The duplicate reviewer decisions were entered side-by-side in an excel spreadsheet to facilitate comparison. The independent reviewers discussed discordant judgments and reconciled them through re-examination of the article. Concordance between reviewer decisions was estimated using percentage agreement, calculated by dividing the number of concordant decisions by the total number of papers reviewed.

Data Extraction Protocol

Reviewers extracted and compiled in tables data on the study methods, population characteristics and estimates of mercury exposure stratified by fish consumption. Data on study methods included: year(s) of data collection; study design; geographic location; participant selection methods; methods used to measure frequency of fish consumption; and laboratory methods used to measure mercury exposure. Population characteristics included distributions of age, sex, ethnicity, heights and weights. EVW created separate tables for each biomarker measured in the included studies. When supplementary information was available for included articles, reviewers inspected it for additional details and included any relevant information in the data tables. Data extraction was also completed in duplicate by independent reviewers (EVW and one trainee) to minimize the likelihood of errors in recording study information. EVW inspected the data compiled by each reviewer and any discrepancies were reconciled through re-examination of the article. In addition to compiling

data presented in the included articles, EVW requested de-identified raw data from corresponding authors with available contact information.

Interpretation of Biomarker Concentration Data

In order to properly interpret results from biomonitoring studies, it is critical to understand the characteristics of the biological medium selected, the toxicokinetic properties of the compound being measured, and how intake of that compound and levels measured in biological tissues or products relate to one another [28,82,85,86,92]. The following sections summarize the toxicokinetic literature pertaining to commonly used matrices in studies on mercury. These concepts guided the interpretation of findings from the literature selected for inclusion in this review.

Blood

Analysis of blood in biomonitoring studies has several advantages. First, concentrations in the blood indicate the current internal dose from all exposure pathways [82,83]. Second, since a primary function of blood is to transport compounds throughout the body, all types of contaminants can be found and measured in blood [82,83]. Further, given that absorbed chemicals may be present in blood prior to reaching sites at which they become biotransformed, analysis of blood allows measurement of the chemical of interest as well as indicators of exposure like metabolites or by-products [82]. However, evidence suggests the level of chemicals like mercury measured in blood may not correlate well with ingested dose [63,69,82,83,93]. One reason for this discrepancy is that concentrations in blood represent the cumulative dose from all exposure pathways [82,83]. This is particularly relevant when the measured compound is total mercury (THg), which people may be exposed to through several routes [63,66–69,71]. Therefore, the strength of the association between fish consumption and THg concentrations in blood would depend on the level of exposure to other sources of mercury in the study population. MeHg is characterized by high lipophilicity, allowing 95-100% of the ingested dose to be absorbed through the gastrointestinal tract into the circulatory system [63,64]. For this reason, blood is considered an appropriate medium for estimating exposure to MeHg [63,64]. Within whole blood, approximately 90% of MeHg is bound to red blood cells, eliminating the need to account for varying serum cholesterol levels in order to accurately measure MeHg levels in a population [63,69]. Further, human exposure to MeHg is almost exclusively through fish consumption [63]. Therefore, MeHg concentrations in blood are thought to correlate well with fish consumption frequency [63].

Another important consideration when interpreting measurements of biomarkers of exposure in blood pertains to the tendency of chemical concentrations to fluctuate considerably in response to a number of factors [82,83,86]. Most notably, time since last exposure exhibits a great deal of influence on the concentration of a compound detected in blood, with recent exposures causing a short spike in concentration that evens out over time [82,83,86]. Therefore, the time at which blood samples are collected heavily impacts the estimated correlation between blood levels and ingested dose [82,83,86]. While the time frame within which samples should be collected is poorly defined, collection within the first 3 days after exposure has been recommended [63]. Methods used to assess fish consumption should correspond with this approximate window. Investigators can specifically inquire about dietary intake in the 3 days preceding blood sample collection in addition to usual consumption patterns to account for variation in chronic exposure. However, validation studies have shown that day to day dietary intake tends to fluctuate to a greater degree than long-term intake [28]. Therefore, results from each of these dietary assessment methods may not correspond with one another. If consumption of fish in the days preceding blood sample collection does not reflect typical long-term intake, the blood mercury concentrations will not be representative of average exposure levels. For this reason, the short window following exposure within which measurements in blood are reliable is a major limitation of this tissue for use in biomonitoring studies.

Further, toxicokinetic evidence suggests variability in the half-life of mercury in blood due to chronicity of exposure, with longer half-lives corresponding to acute exposures relative to chronic exposure [63,69]. Assuming individuals who consume fish more regularly can be considered chronically exposed, relative to those who consume fish less often, failure to account for the subsequent differences in the rate of whole-body elimination and time since last exposure could lead to inappropriate conclusions about the extent to which study participants are exposed to mercury through fish.

Urine

Wastes filtered out of the body by the kidneys include by-products of normal metabolic processes as well as drugs and environmental toxins [94]. Therefore, urine presents an opportunity to quantify exposure to chemicals that are processed by the kidneys. In general, the amount of the compound or its metabolites in urinary samples reflects recent exposure, although the extent to which this holds true is dependent on the toxicokinetic properties of

the chemical of interest [82,85]. Urine is most appropriate for measuring exposure to water-soluble compounds, and in particular metal toxicants, including some forms of mercury [82–85,93].

There are three main types of urine samples, classified according to the timing of collection: spot urine; first morning; and 24-hour [28,82,85]. Spot urine samples are those collected once for each participant, without standardizing collection in relation to a specific time point [28,82,85]. First morning samples are spot samples taken during the first urination of the day [28,82,85]; 24-hour urine samples are those collected multiple times from each participant at standardized times throughout a full day [28,82,85]. The optimal sampling method depends on the analyte of interest, pattern of exposure, predicted concentration of the analyte in urine samples, and the study population [82]; 24-hour urine samples are considered the gold standard in studies aiming to measure absolute intake of substances that are excreted via urine in 24-hour cycles [95]. For example, collection of 24-hour urine samples is estimated to capture >90% of the sodium ingested before sample collection [95]. Spot samples are advantageous for practical reasons, being easiest to collect [82]. However, without standardizing the timing of collection across participants, measurement of exposure in the study population may be skewed by variability introduced by differences in metabolism and fluid intake [82]. Sources of biological variability in excretion of chemicals via urine include sex, body size, urinary output and kidney health [82]. Adjusting for creatinine is a common way to reduce some of the variability introduced by body size and urinary output [82,96]. However, creatinine excretion may be altered by certain kidney disorders [82,96]. These sources of variability are less of a concern when first morning samples are collected, since the urine is more concentrated [28,82,85]. The influence of kidney damage on biomarkers of mercury exposure in urine can be accounted for with assessment of kidney health, which should include a clinical examination [82].

Hair

Human hairs are filaments that are predominantly composed of dead keratinized cells that are bound together by extracellular proteins [94,97]. The rate at which the hair filament grows is dependent on a number of factors, including: anatomic location; age; genetics; sex; health status; and exposure to certain medications [82,92,94,98]. It is estimated that among healthy individuals, the growth rate of scalp hair ranges from 0.6 to 3.36 cm/month, with an average rate of approximately 1 cm/month [82,92,94,98]. Hair is an attractive medium for measuring biomarkers of chemical exposure for a number of reasons. First, depending on

the average length of the hair shaft among study participants and assuming a growth rate of 1 cm/month, analysis of hair can provide information on exposures occurring over a period of up to 1 year [82,83,92,98]. Second, due to the hair growth cycle, characterized by rapid growth (during which chemicals can become incorporated into the tissue) followed by apoptosis, segmental analysis of hair can yield information on short- and long-term exposures as well as patterns of exposure over time [85,92,98,99].

There are three main proposed pathways through which chemical compounds become incorporated in hair filaments [85,92,98,99]. These mechanisms include: passive diffusion from blood during formation of the filament; absorption of chemicals present in the ambient environment, in sweat or sebum through the surface of developed filaments; and transfer from bodily structures and tissues surrounding the follicle [85,92,98,99]. The first pathway is most relevant to ingested exposures [98]. Once compounds are introduced to the base of the follicle, they are subsequently bound to the interior of the hair shaft as the cells become completely keratinized [98]. The extent to which chemicals become integrated in hair tissue through this pathway is dependent on the concentration of the compound in the circulatory system, which is strongly correlated with ingested dose [98]. This model provides a theoretical basis for inferences drawn from segmental analysis of hair shafts; specifically that segmental analysis can provide an indication of the ingested dose across specific time points [85,92,98,99].

Statistical Analysis

Variation in internal dose of a given chemical in a population may reflect true differences in exposure patterns, or differences in characteristics that influence an individual's biological response to the exposure [82,84,85,92]. Therefore, an important consideration for proper interpretation of results from biomonitoring studies is biological variation in response to exposures [28,82,85,86,92]. Specific sources of variation in biological response depend on the chemical of interest and biological media selected for analysis [82]. In general, inter-individual variability in biological response may stem from: demographic characteristics; biological or circadian rhythms; genotypic variations that influence toxicokinetics; exposure history (including exposure to the chemical of interest and others); and dietary habits [82,84,85]. For this reason, the main focus of the meta-analyses conducted for this review was assessment of factors associated with heterogeneity and quantification of the extent to which each factor contributed to variation. Specifically, the goals of the statistical analysis were to: 1) describe patterns of mercury exposure in relation to fish consumption frequencies around the world; 2) assess the extent to which the relationship between increasing consumption of fish and

biomarker concentrations of mercury remains consistent across populations represented in the included literature; and 3) identify sources of heterogeneity across results from studies of this relationship. Because of the superior suitability of hair for measuring exposure to MeHg and because most studies included in the review measured mercury in hair, concentrations in this tissue were selected for use in the statistical analysis. To achieve these goals, EVW conducted two analyses: first, analysis of summary data presented in selected papers; and second, analysis of raw data provided by some of the authors of included research.

Analysis of Summary Data

Given that fish consumption frequencies were categorized in diverse ways in the selected literature, comparison across studies was limited to a subset of studies with compatible exposure categories. The categorization that was compatible with the largest number of studies was: <1 fish meal/week; 1-2 fish meals/week; and ≥ 3 fish meals/week. EVW re-analyzed data from the subset of studies for which arithmetic means of mercury concentration could be calculated for these categories. To achieve this, categories were collapsed and pooled weighted means and corresponding standard deviations were calculated for the new categories. Missing data were handled with mean imputation using data from appropriate surrogate data extracted from the reviewed literature [88,100]. Simulation studies have demonstrated that means of SDs estimated using data from a number of studies included in a systematic review closely approximate actual values for a given study and therefore can be used in situations when there is a small amount of missing data and a sufficient number of studies with complete data from which to estimate mean values [88,100]. The category-specific sample sizes, pooled means and standard deviations were then used to calculate 95% confidence intervals (CIs). Category-specific means and 95% CIs from each study were plotted, to allow for a visual comparison of the findings across studies.

The analysis of summary data examined characteristics of the studies and their respective populations as potential sources of heterogeneity. Relevant characteristics included geographic location, year of data collection, distribution of age and sex in the study population, and methodological features that varied across studies such as methods used to select participants, measure dietary intake of fish or seafood and measure hair-mercury concentrations. The availability of information on these characteristics in study reports determined which characteristics could be examined. Additionally, this analysis was limited

to characteristics that varied sufficiently across studies. Two distinct approaches assessed the extent to which these factors contributed to the heterogeneity across study findings in two ways. First, EVW stratified studies according to the aforementioned characteristics, created stratum-specific graphs of means and 95% CIs, and inspected stratum-specific graphs to assess whether heterogeneity was reduced within subgroups of studies relative to between subgroups. Second, EVW calculated study-specific outcomes, defined as differences in mean THg (µg/g) and corresponding standard errors (SEs) for the following exposure contrasts: 1-2 vs. <1 fish meals/week; and ≥ 3 vs. 1-2 fish meals/week. This approach to defining exposure contrasts is referred to as incremental coding, comparing each category to the one that directly preceded it [86,91]. Incremental coding has been recommended for use in categorical analyses aiming to assess the presence and shape of dose-response relationships [86,91]. In this context, a dose-response hypothesis is supported by the data if those with the lowest level of consumption have lower hair THg concentrations than those with medium consumption and those with high consumption have higher hair THg concentrations than those with medium consumption [91].

A multivariate random-effects meta-regression model estimated SDs and 95% CIs as measures of between-study heterogeneity for both outcomes simultaneously[101]. The correlation between the two outcomes in the model (Y_1: difference in mean THg (µg/g) between those eating 1-2 vs. <1 fish meals/week; Y_2: difference in mean THg (µg/g) between those eating ≥ 3 vs. 1-2 fish meals/week) was calculated using the formula in figure 4 [102]. The random effect represents variation in slope for each exposure contrast, allowing each study to vary with respect to the magnitude and direction of change in mean µg/g THg across categories of fish consumption frequency. The magnitude of the SD represents the average degree to which study-specific effects vary from the population mean. This value is directly comparable to beta-coefficients estimated for independent variables in the model and can be used to assess the relative importance of covariates and combined unmeasured effects of clustering. The multivariate random-effects model included study characteristics to estimate the extent to which they explain heterogeneity across studies for both outcomes [86,103].

Figure 4: *Equation used to estimate the correlation between Y_1 and Y_2 for the multivariate random-effects meta-regression model*

$$\frac{\mathrm{Cov}(Y_1, Y_2)}{\sqrt{\mathrm{Var}(Y_1)*\mathrm{Var}(Y_2)}}$$

Analysis of Raw Data

Analysis of data presented in published literature can provide insight into factors associated with heterogeneity across studies. However, such analyses are limited to assessment of characteristics measured at the study level, which may not correlate well with effects at the individual level [86,103]. To further explore factors that influence the relationship between increasing fish consumption and biomarker concentrations of THg, EVW requested raw data from authors of papers selected for inclusion in the systematic review [104–112]. She tabulated variable distributions from the raw datasets and reviewed the corresponding codebooks to determine the best approach for pooling the data. She assigned each study an ID number, to facilitate statistical adjustment for clustering of individuals in studies. The statistical analysis aimed to estimate the effect of fish consumption frequency on THg level measured in hair, adjusting for socio-demographic characteristics.

A multi-level linear regression model estimated beta-coefficients and 95% CIs as measures of association. Beta-coefficients from this model represent the average change in the expected value of THg (µg/g) corresponding to a change in a covariate value relative to its reference value. Clustering in studies was modeled as a random intercept. Additionally, a random effect was fitted for the slope, representing the magnitude and direction of change in THg (µg/g) for each category of fish consumption frequency. The inclusion of a random slope allows each study to vary with respect to the shape of this relationship. This approach yields a quantitative estimate of the extent to which the relationship between fish consumption and hair THg remains constant across studies. Sensitivity analyses assessed the extent to which modeling decisions altered inferences drawn from the analysis [86]. The fit of the models with and without product terms for interactions between fish consumption frequency and other variables in the model were compared using the Likelihood-ratio test. Additionally, the degree to which the chosen category boundaries for the fish consumption

frequency variable impacted conclusions about residual heterogeneity across studies was assessed by generating additional models with alternate category boundaries and comparing the model estimates.

Indicators of Study Quality and Bias Analysis

Methodological features of the reviewed studies were assessed as potential sources of heterogeneity across studies, and also to provide insight into the likely degree of systematic error and the validity of comparing results across studies. Study quality indicators included methods used to select participants, measure dietary intake of fish or seafood, and measure hair-mercury concentrations. The influence of study methods on within-study validity and comparison validity was assessed in the studies that were included in the meta-analyses. Studies were not excluded from the analyses based on their methodological features, given the potential for exclusion to generate selection bias in the meta-analyses [86]. Instead, statistical models included study quality indicator variables. Given that heterogeneity across study results may be due in part to systematic bias within studies and invalid comparisons across studies, this analysis was used to quantify the extent to which study methods explained heterogeneity across studies, as measured by the SD [86].

Study quality indicators pertaining to participant selection included whether the investigators restricted participation to a specific subset of the population and whether populations that regularly consume large quantities of fish were targeted for participation. Indicators pertaining to exposure classification included the methods used to measure dietary intake of fish and the use of trained interviewers. Indicators pertaining to outcome measurement included whether hair sample lengths were standardized to correspond to a specified exposure period and the laboratory methods used to analyze the hair samples. Only study quality indicators that varied across studies were included in analyses.

Results

After removing duplicates from the identified abstracts, reviewers examined 1691 for eligibility (figure 5). Of those, 364 articles qualified for full text review. There was a high level of agreement between the two reviewers, with 87% (315/363) of the decisions being the same. The predominant reason for exclusion of articles during full-text review was presentation of only beta-coefficients for the effect of increasing fish consumption on biomarker concentrations of mercury. Through this process, 87 papers were selected for

inclusion in the systematic review. None of the 87 study reports were based on the same dataset, except for multiple analyses of National Health and Nutrition Examination Survey data from the United States, each of which used a different subset of the data [113–115]. Study characteristics and mercury concentrations stratified by seafood consumption frequency are presented in tables 2-6.

General Study Characteristics

Of the included studies, the most common study design was cross-sectional (82%; 71/87), followed by prospective cohort (10%; 8/87) (tables 2-6). However, among studies classified in study reports as prospective, only 1 study had multiple measurements of fish or seafood intake and tissue concentrations of mercury taken at regular intervals throughout the follow-up period [106]. The remaining studies were prospective with respect to other health outcomes, but dietary intake and biomarker concentrations were measured once at baseline. The research summarized in the reviewed papers was conducted in 32 countries, spanning 5 continents (Figure 6). The population of the United States was highly represented in the review, with 21 studies conducted in that country. Hair was the most commonly used matrix for biochemical measurement of mercury exposure (67 studies). A smaller number of studies measured mercury concentrations in blood (25 studies) and very few studies measured mercury concentrations in urine (4 studies). Mercury was measured in more than one matrix in 9 studies. Of these, 6 measured mercury concentrations in both hair and blood and 3 measured mercury in both blood and urine. THg was most often reported, with MeHg concentrations in hair or blood reported in only 2 and 4 studies, respectively.

Figure 5: *Study selection flow diagram*

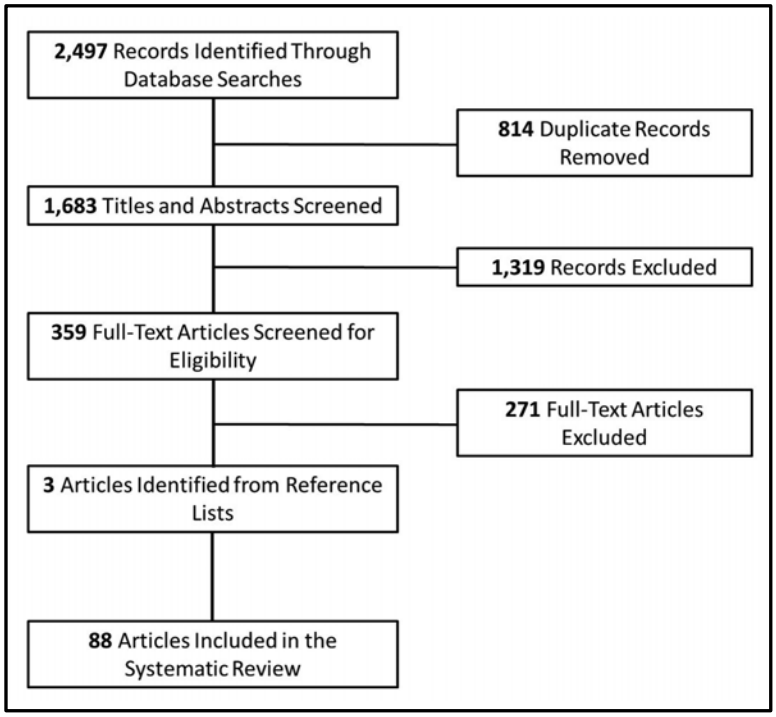


Figure 6: *Geographic distribution of the studies included in the review*

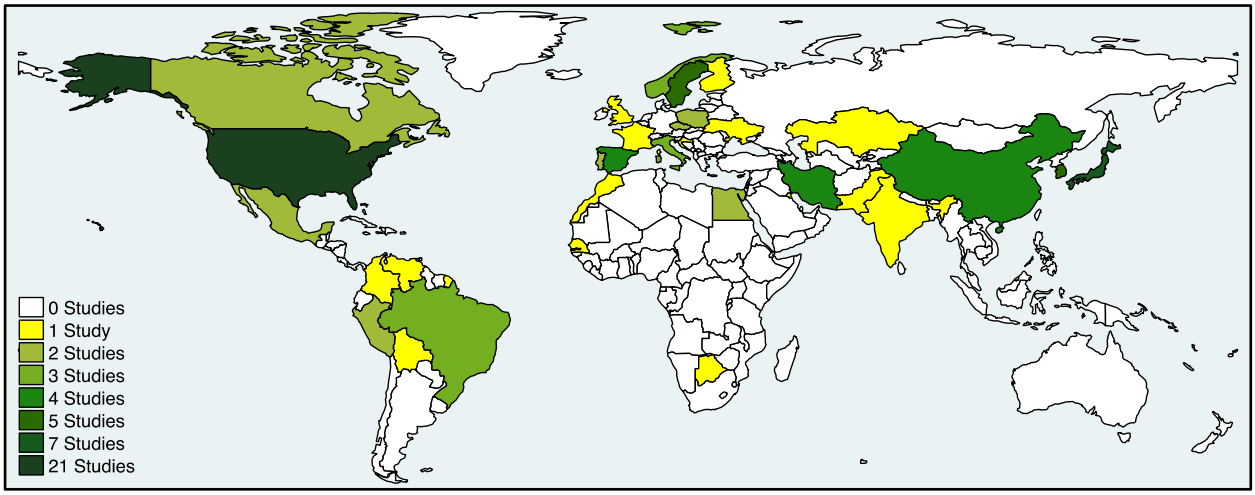


Table 2: *Total mercury concentrations measured in hair, stratified by fish consumption frequency*

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Yamaguchi *et al.* (1971) [116]								
					[Range]			***[Mean±SD (µg/g)]***
CS	Japan	Diet Observed for 10 Days	CV-AAS	410	10-60	F (116) M (294)	≤ 1 meal/day >1 meal/day	3.71 ± 2.13 5.78 ± 2.13
Chen *et al.* (1990) [117]								
					[Mean]		***[Permanently Waved]***	***[Mean±SD (µg/g)]***
CS	Japan	FCF Question(s) on a Multipurpose Questionnaire	CV-AAS	106	42	F (53) M (53)	***[Husbands]*** ≤ 6 meals/week (37) ≥ 7 meals/week (13) ***[Wives]*** ≤ 6 meals/week (37) ≥ 7 meals/week (13) ***[Not Permanently Waved]*** ***[Husbands]*** ≤ 6 meals/week (13) ≥ 7 meals/week (6) ***[Wives]*** ≤ 6 meals/week (13) ≥ 7 meals/week (6)	 3.43 ± 1.077 5.15 ± 2.161 1.67 ± 0.604 3.00 ± 1.152 3.51 ± 1.510 5.23 ± 2.356 1.97 ± 0.709 3.06 ± 0.952
Grandjean *et al.* (1992) [118]								
					[Range]			***[Median (50% Range) nmol/g]***
CS	Faroe Islands (Norway)	FCF Question(s) on a Multipurpose Questionnaire	AA	1,020	20-50	F	0 meals/week (27) 1 meals/week (141) 2 meals/week (365) 3 meals/week (295) 4 meals/week (158) ≥ 5 meals/week (33)	7.0 (2.7-16.3) 16.8 (7.3-32.1) 22.6 (12.8-36.6) 25.2 (13.9-41.8) 26.0 (15.6-40.4) 25.1 (16.0-42.6)
Oskarsson *et al.* (1994) [119]								
							[Close to Smelter]	***[Mean±SD (µg/g)]***
PC	Sweden	FCF Question(s) on a Multipurpose Questionnaire	CV-AAS	197	ND	F	<1 meal/month (98) 1-3 meals/month (18) ≥ 1 meal/week (8) ***[Away from Smelter]*** <1 meal/month (53) 1-3 meals/month (21) ≥ 1 meal/week (5)	0.24 ± 0.11 0.34 ± 0.13 0.35 ± 0.15 0.30 ± 0.17 0.32 ± 0.19 0.55 ± 0.11

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Salonen *et al.* (1995) [120]								
					[Range]		***[Rural - Burbot]***	***[Mean (µg/g)]***
PC	Finland	Food Diaries (4 Days)	CV-AAS	1, 833	42-60	M	Doesn't eat Burbot	2.22
							Eats Burbot	3.83
							[Urban - Burbot]	
							Doesn't eat Burbot	1.91
							Eats Burbot	2.53
							[Rural - Vendace]	
							Doesn't eat Vendace	2.09
							Eats Vendace	3.46
							[Urban - Vendace]	
							Doesn't eat Vendace	1.87
							Eats Vendace	2.60
							[Rural - Northern Pike]	
							Doesn't eat Northern Pike	2.24
							Eats Northern Pike	3.19
							[Urban - Northern Pike]	
							Doesn't eat Northern Pike	1.96
							Eats Northern Pike	2.63
							[Rural - Whitefish]	
							Doesn't eat Whitefish	2.23
							Eats Whitefish	2.33
							[Urban - Whitefish]	
							Doesn't eat Whitefish	1.84
							Eats Whitefish	2.92
							[Rural - Walleye]	
							Doesn't eat Walleye	2.42
							Eats Walleye	1.13
							[Urban - Walleye]	
							Doesn't eat Walleye	2.07
							Eats Walleye	2.40
							[Rural - Bream]	
							Doesn't eat Bream	2.32
							Eats Bream	2.18

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Salonen *et al.* (1995) (*Continued*) [120]								
					[Range]		***[Urban - Bream]***	***[Mean (µg/g)]***
PC	*Finland*	*Food Diaries (4 Days)*	*CV-AAS*	*1, 833*	*42-60*	*M*	Doesn't eat Bream	1.96
							Eats Bream	2.14
							[Rural - Perch]	
							Doesn't eat Perch	2.35
							Eats Perch	2.23
							[Urban - Perch]	
							Doesn't eat Perch	1.99
							Eats Perch	2.01
							[Rural - Salmon]	
							Doesn't eat Salmon	2.28
							Eats Salmon	2.18
							[Urban - Salmon]	
							Doesn't eat Salmon	1.90
							Eats Salmon	2.26
							[Rural - Baltic Herring]	
							Doesn't eat Baltic Herring	2.25
							Eats Baltic Herring	2.68
							[Urban - Baltic Herring]	
							Doesn't eat Baltic Herring	1.92
							Eats Baltic Herring	2.11
							[Rural - Herring]	
							Doesn't eat Herring	2.28
							Eats Herring	2.04
							[Urban - Herring]	
							Doesn't eat Herring	1.90
							Eats Herring	2.10
							[Rural - Rainbow Trout]	
							Doesn't eat Rainbow Trout	2.18
							Eats Rainbow Trout	2.30
							[Urban - Rainbow Trout]	
							Doesn't eat Rainbow Trout	1.82
							Eats Rainbow Trout	2.0

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Salonen *et al.* (1995) (*Continued*) [120]								
					[Range]		***[Rural - Saithe]***	***[Mean (µg/g)]***
PC	*Finland*	*Food Diaries (4 Days)*	*CV-AAS*	*1, 833*	*42-60*	*M*	Doesn't eat Saithe	2.22
							Eats Saithe	2.78
							[Urban - Saithe]	
							Doesn't eat Saithe	1.91
							Eats Saithe	1.81
							[Rural - Tuna]	
							Doesn't eat Tuna	2.05
							Eats Tuna	1.93
							[Urban - Tuna]	
							Doesn't eat Tuna	1.70
							Eats Tuna	1.42
Buzina *et al.* (1995) [121]								
					[Range]			***[Mean±SD (µg/g)]***
CS	Croatia	Food Diaries (2 Weeks)	CV-AAS	92	2-83	F (45)	0-999 g/week (51)	4.91 ± 3.15
						M (47)	1000-1500 g/week (23)	6.56 ± 4.67
							>1500 g/week (17)	6.39 ± 3.51
Batista *et al.* (1996) [122]								
					[Range]			***[Mean (µg/g)]***
CS	Spain	FCF Question(s) on a Multipurpose Questionnaire	CV-AAS	233	6-16	F (154)	0 meals/week (5)	0.45
						M (79)	1 meals/week (113)	0.66
							2 meals/week (85)	0.80
							3 meals/week (25)	1.25
							4 meals/week (5)	1.93
Weihe *et al.* (1996) [123]								
					[Range]		***[Whale Consumption]***	***[Median (50% Range) nmol/g]***
CS	Faroe Islands	FCF Question(s) on a Multipurpose Questionnaire	AA	1,020	20-50	F	None (208)	11.2 (5.8-21.0)
							1 meal/month (285)	18.8 (12.6-30.9)
							2 meals/month (249)	24.6 (15.2-38.5)
							3 meals/month (88)	35.1 (20.7-47.5)
							≥ 4 meals/month (183)	35.3 (23.9-55.9)
Smith *et al.* (1997) [124]								
					[Range]			***[Geometric mean ± SD (µg/g)]***
PC	USA	Food Diaries (1 year)	GC	2,000	15-45	F	No Seafood (1,274)	0.24 ± 2.6
							Some Seafood (1,546)	0.36 ± 2.5

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Cordier *et al.* (1998) [125]								
					[Range]			***[Geometric Mean ± SD (µg/g)]***
CS	French Guiana	General FFQ	CV-AAS	391	14-80	F (131) M (124)	0 meals/week (5) 1-2 meals/week (142) 3-4 meals/week (91) ≥ 5 meals/week (77)	0.7 ± 0.48 1.7 ± 1.51 3.2 ± 2.88 6.2 ± 4.19
Murata *et al.* (1999) [126]								
					Mean (Range)			***[Mean (µg/g)]***
CS	Portugal	Diet Questions on a Multipurpose Questionnaire	CV-AAS	149	6.9 (6.4-7.4)	F	< 1 meals/week (36) 2 meals/week (37) 3 meals/week (25) 4 meals/week (17) ≥ 5 meals/week (32)	8.49 8.62 9.87 10.23 11.91
Dickman *et al.* (1999) [127]								
					[Range]			***[Mean (µg/g)]***
CS	China	FCF Question(s) on a Multipurpose Questionnaire	ICP-MS	211	24-75	F (97)	≤ 3 meals/week (55) ≥ 4 meals/week (42)	2.71 3.76
						M (117)	≤ 3 meals/week ≥ 4 meals/week	3.74 5.38
Hacon *et al.* (2000) [128]								
					[Range]			***[Mean (µg/g)]***
CS	Brazil	FCF Question(s) on a Multipurpose Questionnaire	CV-AAS	75	14-45	F	Non-consumer (23) Consumer (52)	0.62 1.23
Al-Majed and Preston (2000) [110]								
					[Range]			***[Mean ± SD (µg/g)]***
CS	Kuwait	FCF Question(s) on a Multipurpose Questionnaire	HV-AFS	135	16-58	M	0 meals/week (10) 1 meals/week (14) 2 meals/week (11) 3 meals/week (2) 4 meals/week (12) 7 meals/week (70) 14 meals/week (5) 21 meals/week (11)	0.96 ± 0.15 2.48 ± 0.45 4.30 ± 0.71 7.31 ± 6.44 4.72 ± 4.9 3.66 ± 2.27 3.95 ± 2.11 6.45 ± 4.96
Kosatsky *et al.* (2000) [129]								
					Mean ± SD			***[Mean ± SD (µg/g)]***
CS	Canada	Fish-Focused FFQ	CV-AAS	132	46.7 ± 14	F (16) M (116)	<1 meal/week (72) ≥ 1 meal/week (60)	0.38 ± 2.28 0.82 ± 2.54

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
de Oliveira Santos *et al.* (2000) [130]								
					Cat (n)		***[Average Meals/Week]***	***[Mean ± SD (µg/g)]***
CS	Brazil	FCF Question(s) on a Multipurpose Questionnaire	AAS	894				
	Sao Luiz do Tapajos				0-20 (221) 21-40 (66) 41-60 (32) > 60 (8)		12 meals/week (20) 13 meals/week (78) 14 meals/week (229)	14 ± 7.6 20.7 ± 14.4 20.2 ± 11.3
	Santana de Ituqui				0-20 (205) 21-40 (70) 41-60 (35) > 60 (11)		11 meals/week (37) 12 meals/week (119) 13 meals/week (88) 14 meals/week (77)	3.67 ± 1.84 4.4 ± 1.9 4.4 ± 1.9 4.5 ± 2.0
	Brasilia Legal				0-10 (86) 11-15 (24) 16-25 (13) 26-35 (14) 36-55 (15)		9 meals/week (24) 10 meals/week (115) 12 meals/week (13)	12.41 ± 6.1 10.9 ± 7.4 14.2 ± 8.4
McDowell *et al.* (2004) [115]								
					[Range]		***[Fish-past 30 days]***	***[Mean (95%CI) (µg/g)]***
SCS	USA	Fish-Focused FFQ	CV-AAS	838	1-5	F M	None (354) 1-2 meals (221) ≥ 3 meals (208)	0.13 (0.11, 0.14) 0.21 (0.17, 0.24) 0.40 (0.24, 0.55)
							[Shellfish-past 30 days]	
							None (587) ≥ 1 meal (195)	0.21 (0.17, 0.24) 0.27 (0.17, 0.36)
					[Range]		***[Fish-past 30 days]***	
				1726	16-49	F	None (639) 1-2 meals (573) ≥ 3 meals (447)	0.25 (0.11, 0.38) 0.36 (0.28, 0.43) 0.77 (0.59, 0.94)
							[Shellfish-past 30 days]	
							None (878) ≥ 1 meal (782)	0.26 (0.20, 0.31) 0.64 (0.50, 0.77)

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Johnsson *et al.* (2004) [109]								
CS	Sweden	General FFQ	CVAF	143	***Mean (Range)*** 61 (19-97)	F (51)		***[Mean (µg/g)]***
							< 1 meal/month (19)	0.5
							≥ 1 meal/month; <1 meal/week (32)	1.4
							≥ 1 meal/week; <2 meals/week (16)	1.8
							≥ 2 meals/week (4)	2.3
						M (920)		
							< 1 meal/month (20)	0.5
							≥ 1 meal/month; <1 meal/week (72)	2.4
							≥ 1 meal/week; <2 meals/week (29)	3.1
							≥ 2 meals/week (9)	4.6
Bjornberg *et al.* (2005) [131]								
CS	Sweden	General FFQ	CV-AAS	127	***Median (Range)*** 38 (19-45)	F		***[Mean (µg/g)]***
							0 meals/week (26)	0.57
							1 meal/week (87)	0.69
							>1 meal/week (13)	0.89
Xue *et al.* (2007) [108]								
PC	USA	FCF Question(s) on a Multipurpose Questionnaire	CV-AAS	1,024	***Cat (n)*** <25 (422) ≥25 (602)	F		***[Mean (µg/g)]***
							0 meals/6 months (109)	0.13
							1-5 meals/6 months (267)	0.20
							6-23 meals/6 months (347)	0.25
							≥ 24 meals/6 months (288)	0.28
Knobeloch *et al.* (2007) [132]								
CS	USA	General FFQ	EPA Method 631	2,028	***Mean (Range)*** 49.4 (18-92)	F (1050) M (978)	***[Has Fishing License]***	***[Median (µg/g)]***
							0 meals/month (26)	0.1
							1-2 meals/month (56)	0.453
							3-4 meals/month (183)	0.718
							5-6 meals/month (196)	0.726
							7-8 meals/month (191)	0.961
							9-10 meals/month (125)	0.992
							11-12 meals/month (95)	1.073
							13-14 meals/month (66)	1.05
							≥ 15 meals/month (104)	1.09

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Knobeloch *et al.* (2007) *(Continued)* [132]								
CS	USA	General FFQ	EPA Method 631	2,028	***Mean (Range)*** 49.4 (18-92)	F (1050) M (978)	***[No Fishing License]*** 0 meals/month (69) 1-2 meals/month (119) 3-4 meals/month (221) 5-6 meals/month (160) 7-8 meals/month (129) 9-10 meals/month (78) 11-12 meals/month (79) 13-14 meals/month (39) ≥ 15 meals/month (92)	***[Median (µg/g)]*** 0.085 0.258 0.366 0.498 0.618 0.589 0.851 0.744 1.453
Elhamri *et al.* (2007) [105]								
CS	Morocco	FCF Question(s) on a Multipurpose Questionnaire	CV-AAS	108	***Mean (Range)*** 34 (10-61)	F (40) M (68)	0 meals/week 1 meal/week 2 meals/week 3 meals/week 4 meals/week 5 meals/week	***[Mean (µg/g)]*** 0.29 1.04 1.7 3.69 6.68 9.23
Anwar *et al.* (2007) [133]								
CS	Pakistan	FCF Question(s) on a Multipurpose Questionnaire	CV-AAS	158	***Cat (n)*** 1-20 (23) 21-30 (87) ≥ 31 (48)	F (75) M (83)	< 1 meal/week (65) 1-2 meals/week (22) ≥ 3 meals/week (21)	***[Mean (µg/g)]*** 0.17 0.20 0.20
Marques *et al.* (2007) [134]								
CS	Brazil	General FFQ	CV-AAS	100	***Median (Range)*** 22 (15-40)	F	0 -1 meals/week (57) ≥ 2 meals/week (43)	***[Mean (µg/g)]*** 3.5 5.7
Rojas *et al.* (2007) [135]								
CC	Venezuela	FCF Question(s) on a Multipurpose Questionnaire	AAS	160	***Mean ± SD*** 47.5 ± 14.7	F (74) M (86)	***[Retired Workers]*** 1-3 meals/week (2) 2-5 meals/week (16) ≥ 7 meals/week (2) ***[Current Workers]*** 0 meals/week (1) 1-3 meals/week (6) 2-5 meals/week (6)	***[Mean ± SD (µg/g)]*** 0.4 ± 0.2 1.8 ± 1.8 0.6 ± 0.3 0.6 2.4 ± 1.3 1.8 ± 0.4

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Rojas *et al.* (2007) *(Continued)* [135]								
CC	Venezuela	FCF Question(s) on a Multipurpose Questionnaire	AAS	160	***Mean ± SD*** 47.5 ± 14.7	F (74) M (86)	***Residents of:*** ***[A Fishing Village]*** 0 meals/week (1) 1-3 meals/week (2) 2-5 meals/week (3) ≥ 7 meals/week (8) ***[Puerto Cabello]*** 0 meals/week (1) 1-3 meals/week (4) 2-5 meals/week (8) ***[Valencia]*** 0 meals/week (64) 1-3 meals/week (25) 2-5 meals/week (9) ≥ 7 meals/week (2)	***[Mean ± SD (µg/g)]*** 0.3 0.4 ± 0.1 1.8 ± 0.9 3.5 ± 0.9 0.9 1.0 ± 0.4 1.8 ± 1.6 0.91 ± 0.76 1.20 ± 1.09 1.02 ± 0.98 0.79 ± 0.57
Diez *et al.* (2008) [136]								
CS	Italy	FCF Question(s) on a Multipurpose Questionnaire	GF-AAS		***[Mean ± SD]*** 39.9 ± 2.6	F M	0 meals/week 1-2 meals/week 3-4 meals/week 5-6 meals/week	***[Mean (µg/g)]*** 0.464 No Data No Data 0.906
Park *et al.* (2008) [137]								
CS	Korea	Not Specified	Mercury Analyzer SP-3DS	125	***Cat (n)*** 6-9 (60) 10-12 (65)	F (50) M (75)	0 meals/week (11) 1 meal/week (38) 2-3 meals/week (60) 4-6 meals/week (9) ≥ 7 meals/week (2)	***[Mean ± SD (µg/g)]*** 0.60 ± 0.14 0.73 ± 0.30 0.84 ± 0.36 1.04 ± 0.60 0.85 ± 0.15
	China	*Not Specified*	*Mercury Analyzer SP-3DS*	372	***Cat (n)*** 6-9 (184) 10-12 (185)	F (216) M (156)	0 meals/week (113) 1 meal/week (161) 2-3 meals/week (38) 4-6 meals/week (8) ≥ 7 meals/week (2)	***[Mean ± SD (µg/g)]*** 0.13 ± 0.09 0.17 ± 0.12 0.17 ± 0.15 0.13 ± 0.12 0.24 ± 0.05

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Kruzikova *et al.* (2008) [138]								
					[Range]		***[Marine Fish]***	***[Mean (µg/g)]***
CS	Czech Republic	FCF Question(s) on a Multipurpose Questionnaire	CV-AAS	311	2-66	F (251) M (60)	None (26) Sometimes (95) Often (93) Several times a month (86) Several times a week (11)	0.113 0.159 0.247 0.254 1.163
							[Freshwater Fish]	
							None (46) Rarely (232) Once a month (33)	0.303 0.214 0.366
Karouna-Renier *et al.* (2008) [107]								
					Cat (n)		***[# meals past 30 days]***	***[Mean (µg/g)]***
CS	USA	FCF Question(s) on a Multipurpose Questionnaire	CV-AFS	601	15-19 (25) 20-29 (187) 30-39 (185) 40-49 (204)	F	0 (82) 1 (96) 2 (119) 3 (93) ≥ 4 (210)	0.08 0.19 0.20 0.29 0.47
							[#meals past 2 months]	
							0 (93) 1 (89) 2 (131) 3 (92) ≥ 4 (196)	0.10 0.15 0.22 0.36 0.45
Diez *et al.* (2009) [139]								
					[Range]			***[Mean ± SD (µg/g)]***
CS	Spain	General FFQ	CV-AFS	218	0-4	F (121) M (97)	0 meals/week (6) 1-2 meals/week (56) 3-4 meals/week (23) > 4 meals/week (15)	0.49 No Data No Data 1.4
Barbieri *et al.* (2009)[140]								
					Cat (n)			***[Mean (µg/g)]***
CS	Bolivia	General FFQ	CV-AAS	150	1-15 (68) 16-35 (45) ≥ 36 (37)	F (77) M (73)	< 7 meals/week (47) 7-13 meals/week (46) ≥ 14 meals/week (57)	2.29 3.38 3.45

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Salehi and Esmaili-Sari (2010) [141]								
CS	Iran	Standardized Questionnaire to Measure Nutrition Status	AMA Mercury Analyzer	149	***Mean ± SD*** 24.4 ± 4.7	F	1 meal/week (22) 2 meals/week (45) 3 meals/week (47) ≥ 4 meals/week (35)	***[Mean (µg/g)]*** 1.89 2.41 4.25 4.83
Puklova *et al.* (2010) [142]								
PC	Czech Republic	FCF Question(s) on a Multipurpose Questionnaire	AMA Mercury Analyzer	316	Children	F M	Never ≥ 1 meal/week	***[Median]*** 0.15 0.2
Agah *et al.* (2010) [111]								
CS	Iran	FCF Question(s) on a Multipurpose Questionnaire	CV-AAS	19	***[Range]*** 18-54	M	2 meals/week (1) 3 meals/week (4) 4 meals/week (3) 5 meals/week (1) 6 meals/week (4) 7 meals/week (3) 11 meals/week (1)	***[Mean ± SD (µg/g)]*** 0.8 1.95 ± 0.58 2.83 ± 2.33 1.0 4.18 ± 2.66 3.36 ± 2.85 39.5
Fakour *et al.* (2010) [143]								
RC	Iran	FCF Question(s) on a Multipurpose Questionnaire	LECO AMA 254	195	***Mean ± SD*** 31.3 ± 3.12	F	<3 meals/month (49) >7 meals/month (53)	***[Mean ± SD (µg/g)]*** 0.86 ± 0.42 3.79 ± 1.89
El-Baz *et al.* (2010) [144]								
CC	Egypt	FCF Question(s) on a Multipurpose Questionnaire	AAS	32	***Cat (n)*** < 5 (11) 5-9 (14) > 9 (7)	F (10) M (22)	Doesn't Eat Fish Eats Fish	***[Mean ± SD (µg/g)]*** 0.750 ± 0.501 1.103 ± 0.564
Lim *et al.* (2010) [145]								
CS	South Korea	General FFQ	DMA	1,589	***Mean ± SD*** 33 ± 18	F (852) M (737)	< 2 meals/month (353) ≥ 2 meals/month (178)	***[Geometric Mean ± SD (µg/g)]*** 1.06 ± 1.66 1.33 ± 1.86

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Trasande *et al.* (2010) [146]								
CS	Mexico	General FFQ	CV-AAS	92	Child-bearing Age	F	***[Carp]*** < 1 meal/month (47) ≥ 1 meal/month (44) ***[Whitefish]*** < 1 meal/month (49) ≥ 1 meal/month, <1 meal/week (30) ≥ 1 meal/week (8) ***[Fish Soup]*** < 1 meal/month (32) ≥ 1 meal/month, <1 meal/week (33) ≥ 1 meal/week (22) ***[Tilapia]*** < 1 meal/month (32) ≥ 1 meal/month, <1 meal/week (33) ≥ 1 meal/week (22) ***[Catfish]*** < 1 meal/month (52) ≥ 1 meal/month (31) ***[Other Fish]*** < 1 meal/month (47) ≥ 1 meal/month (44)	***[Mean ± SD (µg/g)]*** 0.526 ± 0.536 0.858 ± 0.849 0.551 ± 0.475 0.826 ± 0.898 1.086 ± 1.149 0.604 ± 0.468 0.685 ± 0.620 0.898 ± 1.101 0.704 ± 0.590 0.455 ± 0.452 0.863 ± 0.884 0.577 ± 0.656 0.869 ± 0.821 0.684 ± 0.773 0.696 ± 0.537
Endo & Haraguchi (2010) [147]								
CS	Japan	FCF Question(s) on a Multipurpose Questionnaire	AAS	50	ND	F (20) M (30)	***[Pilot Whale & Dolphin]*** None (11) 1 meal/a few months (11) ≥ 1 meal/month (28)	***[Mean ± SD (µg/g)]*** 4.3 ± 1.7 15.5 ± 10 24.6 ± 15.6

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Hsiao *et al.* (2011) [148]								
CS	Kazakhstan	General FFQ	Mercury Analyzer SP-3	289	***[Range]*** 2-83	F (174) M (113)	0 meals/past year (20) ≥ 1 meal/past year (164)	***[Mean (Range) (µg/g)]*** 0.101 (0.009-0.358) 0.617 (0.015-5.184)
Lincoln *et al.* (2011) [149]								
CS	USA	Semi-Quantitative General FFQ	EPA Method 7473	402	***Cat (n)*** 18-39 (106) 40-54 (176) 55-84 (114)	F (44) M (354)	< 1 meals/week (23) 1-2 meals/week (211) 3 meals/week (158) ≥ 7 meals/week (6)	***[Mean ± SD (µg/g)]*** 0.93 ± 0.8 1.1 ± 1.0 1.2 ± 1.2 2.3 ± 1.5
Olivero-Verbel *et al.* (2011) [150]								
CS	Colombia	FCF Question(s) on a Multipurpose Questionnaire	AAS	1328	***Cat (n)*** < 15 (295) 16-30 (382) 31-50 (468) > 50 (183)	F (757) M (569)	1 meal/week 2 meals/week 3 meals/week 4 meals/week 5 meals/week 6 meals/week 7 meals/week	***[Mean ± SE (µg/g)]*** 1.72 ± 0.19 1.49 ± 0.11 1.47 ± 0.12 1.28 ± 0.11 2.02 ± 0.32 1.27 ± 0.13 1.79 ± 0.08
Black *et al.* (2011) [104]								
CS	Botswana	FCF Question(s) on a Multipurpose Questionnaire	CV-AAS	101	***Mean (Range)*** 29 (4-70)	F (60) M (41)	0-4 meals/month (8) 5-12 meals/month (60) 13-20 meals/month (11) >20 meals/month (22)	***[Mean ± SD (µg/g)]*** 0.08 ± 0.04 0.16 ± 0.19 0.41 ± 0.32 0.29 ± 0.23
Sagiv *et al.* (2012) [151]								
PC	USA	General FFQ	Direct Mercury Analyzer 80	421	***Cat (n)*** <20 (56) 20-29 (209) 30-34 (100) ≥ 35 (56)	F	≤ 2 meals/week (196) > 2 meals/week (217)	***[Mean (Range) (µg/g)]*** 0.55 (0.04-3.27) 0.68 (0.03-5.14)

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Ashe (2012) [152]								
								[Mean (µg/g)]
CS	Peru	FCF Question(s) on a Multipurpose Questionnaire	CV-AFS	204	ND	F (106) M (98)	0-5 meals/month (136) 6-11 meals/month (34) ≥ 12 meals/month (34)	2.02 2.12 3.49
Okati *et al.* (2012) [153]								
					[Range]			***[Mean ± SD (µg/g)]***
CS	Iran	FCF Question(s) on a Multipurpose Questionnaire	LECO AMA 254	186	17-36	F	<1 meal/month (11) 1-2 meals/month (16) 1-2 meals/week (43) >2 meals/week (23)	0.5 ± 0.43 1.28 ± 0.91 3.95 ± 1.74 3.55 ± 2.52
							[Maternal Consumption]	
					≤ 0.5		<1 meal/month (11) 1-2 meals/month (16) 1-2 meals/week (43) >2 meals/week (23)	0.34 ± 0.27 0.48 ± 0.37 2.01 ± 1.44 3.38 ± 2.15
Gari *et al.* (2013) [154]								
					Cat (n)			***[Geometric Mean (µg/g)]***
PC	Spain	General FFQ	ICP-MS	302	< 30 (55) > 30 (45)	F (57) M (43)	Rare or never 1-2 meals/week	0.49 0.99
Traynor *et al.* (2013) [155]								
					Cat (n)			***[Mean (µg/g)]***
CS	USA	FCF Question(s) on a Multipurpose Questionnaire	CGA-AAS	640	18-24 (159) 25-34 (287) 35-49 (252)	F	0 meals/week (63) 1-2 meals/week (292) 3-4 meals/week (204) > 4 meals/week (139)	0.15 0.3 0.42 0.53
Shao *et al.* (2013) [156]								
					[Mean]			***[Mean ± SD (µg/g)]***
CS	China	FCF Question(s) on a Multipurpose Questionnaire	EPA Method 7473	91	33.4		0-1 meals/week (23) 2-4 meals/week (37) > 4 meals/week (40)	0.65 ± 0.37 0.87 ± 0.75 1.58 ± 1.16

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Vieira *et al.* (2013) [157]								
CS	Portugal	FCF Question(s) on a Multipurpose Questionnaire	AAS	110	***Mean (Range)*** 31.4 (3-91)	F (81) M (29)	Never 1-2 meals/week 3-4 meals/ week ≥ 5 meals/week	***[Category Range (µg/g)]*** 0.05-0.61 0.18-2.22 0.41-2.17 0.82-2.24
Seabert *et al.* (2014) [158]								
CS	Canada	Fish-Focused FFQ	CV-AAS	71	***Mean ± SD*** 44.7 ± 14	F M	<1 meal/month (28) <1 meal/week; >1 meal/month (22) ≥ 1 meal/week (21)	***[Mean ± SD (µg/g)]*** 0.8 ± 0.7 1.9 ± 1.8 2.9 ± 1.6S
Xue *et al.* (2014) [159]								
CS	China	Not Specified	Mercury Analyzer NIC MA-3000	301	***Mean ± SD*** 52.5 ± 13.1	F (182) M (119)	***[Has Gastritis (Cases)]*** Doesn't eat fish (84) Eats fish (68) ***[No Gastritis (Controls)]*** Doesn't eat fish (137) Eats fish (12)	***[Mean ± SD (µg/g)]*** 0.856 ± 0.95 0.974 ± 0.8 0.439 ± 0.26 0.697 ± 0.25
Michalak *et al.* (2014) [160]								
CS	Poland	FCF Question(s) on a Multipurpose Questionnaire	AMA 254 Analyzer (AAS)	321	***Mean ± SD*** 25 ± 10	F (206) M (115)	0 meals/week (63) 1 meal/week (185) 2 meals/week (39) 3 meals/week (11) ≥ 4 meals/week (4)	***[Mean ± SD (µg/g)]*** 0.21 ± 0.14 0.13 ± 0.12 0.19 ± 0.13 0.24 ± 0.17 0.41 ± 0.07
Schaefer *et al.* (2014) [161]								
CS	USA	General FFQ	EPA Method 7473	135	***Mean (Range)*** 54 (18-90)	F (62) M (73)	< 1 meals/week (10) 1 meal/week (50) 3 meals/week (66) ≥ 7 meals/week (9)	***[Mean ± SD (µg/g)]*** 0.49 ± 0.29 1.08 ± 1.16 1.95 ± 2.32 2.14 ± 1.86

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Ramos *et al.* (2014) [162]								
					Cat (n)			***[Median (Range)]***
CS	USA	FCF Question(s) on a Multipurpose Questionnaire	DMA	110	< 45 (74) > 46 (36)	F (53) M (57)	¼ lbs. / week (34) ½ lbs. / week (24) 1 lbs. / week (30) > 1 lbs. / week (22)	0.6 (0.02-23.3) 0.9 (0.1-5.5) 1.7 (0.2-6.7) 1.1 (0.1-7.0)
Gaxiola-Robles *et al.* (2014) [163]								
					Mean ± SD		***[Fish Consumption]***	***[Median]***
CS	Mexico	FCF Question(s) on a Multipurpose Questionnaire	DMA	75	26.3 ± 8.1	F	None (7) 1/month (28) 2/month (31) ≥ 2/week (9)	0.6 1.4 1.7 1.9
							[Seafood Consumption]	
							None (23) 1/month (37) 2/month (13) ≥ 2/week (2)	1.3 1.5 2 1.7
Miyashita *et al.* (2015) [a] [164]								
					Mean ± SD			***[Median (µg/g)]***
CS	Japan	FCF Question(s) on a Multipurpose Questionnaire	OC-GA	322	30.6 ± 4.7	F	< 25 g/day 25-38.75 g/day 38.75-50 g/day ≥ 50 g/day ***[Shoreline Fish]*** < 1 meal/week ≥ 1 meal/week ***[Pelagic Fish]*** < 1 meal/week ≥ 1 meal/week	1.5 1.3 1.4 1.7 1.3 1.5 1.3 1.5
Miyashita *et al.* (2015) [b] [165]								
					Mean ± SD			***[Median (Range) (µg/g)]***
CS	Japan	FCF Question(s) on a Multipurpose Questionnaire	OC-GA	367	30.8 ± 4.8	F	***[Shoreline Fish]*** < 1 meal/week (198) ≥ 1 meal/week (169) ***[Pelagic Fish]*** < 1 meal/week (171) ≥ 1 meal/week (196)	 1.31 (0.31-4.35) 1.46 (0.24-4.73) 1.24 (0.24-4.03) 1.49 (0.32-4.73)

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Mohamed *et al.* (2015) [166]								
CC	Egypt	Not Specified	No Data	100	***Mean ± SD*** 6.2 ± 2.4	F (16) M (84)	0 meals/month (0) 1 meal/month (19) 2-4 meals/month (51) > 4 meals/month (0)	***[Mean ± SD (µg/g)]*** - 0.34 ± 0.21 0.37 ± 0.24 -
Niane *et al.* (2015) [167]								
CS	Senegal *Kedougou & Samekouta*	FCF Question(s) on a Multipurpose Questionnaire	AAS	111	***[Range]*** 1-56	F (61) M (50)	 0-1 meals/week 2-4 meals/week	***[Median (µg/g)]*** 0.39 0.38
	Tinkoto & Bantako						0-1 meals/week 2-4 meals/week	0.97 2.4
Helmfrid *et al.* (2015) [168]								
CS	Sweden	General FFQ	ICP-MS	95	***Mean ± SD*** 65 ± 17	F (57) M (38)	Doesn't eat fish (63) Eats fish (32)	***[Mean ± SD (µg/g)]*** 0.40 ± 0.27 1.06 ± 1.22
Bonsignore *et al.* (2015) [112]								
CS	Italy	FCF Question(s) on a Multipurpose Questionnaire	EPA Method 7473	21	***[Range]*** 30-40	F (11) M (10)	< 1 meals/week (3) 1-2 meals/week (15) ≥ 3 meals/week (3)	***[Mean ± SD (µg/g)]*** 1.32 ± 0.94 1.97 ± 0.86 5.1 ± 0.24
Buchanan *et al.* (2015) [169]								
CS	USA	FCF Question(s) on a Multipurpose Questionnaire	CV-AAS	41	***Mean ± SD*** 53.5 ± 14.1	F (47) M (23)	***[Tuna Fish]*** Doesn't eat Tuna Eats Tuna ***[Catfish]*** Doesn't eat Catfish Eats Catfish	***[Geometric Mean (µg/g)]*** 0.45 0.76 0.5 0.8
Dong *et al.* (2015) [a] [106]								
PC	USA	FCF Question(s) on a Multipurpose Questionnaire	AAS	152	***Median*** 54	F (69) M (83)	***[Visit 1]*** 0 meals/past 3 months (1) 1 meal/past 3 months (8) 1 meal/month (16) 2-3 meals/month (53) 1 meal/week (44) 2-3 meals/week (25) 4-6 meals/week (4) ≥ 7 meals/week (1)	***[Mean ± SD (µg/g)]*** 0.058 0.148 ± 0.182 0.119 ± 0.098 0.247 ± 0.345 0.298 ± 0.397 0.412 ± 0.424 1.189 ± 1.30 0.581

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Dong *et al.* (2015) [a] (*Continued*) [106]								
					Median		***[Visit 2]***	***[Mean ± SD (µg/g)]***
PC	*USA*	*FCF Question(s) on a Multipurpose Questionnaire*	*AAS*	*152*	*54*	*F (69)* *M (83)*	0 meals/past 3 months (1) 1 meal/ past 3 months (1) 1 meal/month (11) 2-3 meals/month (45) 1 meal/week (36) 2-3 meals/week (20) 4-6 meals/week (4) ≥ 7 meals/week (0)	0.055 0.087 0.106 ± 0.087 0.315 ± 0.560 0.396 ± 0.405 0.336 ± 0.285 0.268 ± 0.111 -
							[Visit 3]	
							0 meals/past 3 months (0) 1 meal/ past 3 months (8) 1 meal/month (15) 2-3 meals/month (31) 1 meal/week (25) 2-3 meals/week (23) 4-6 meals/week (2) ≥ 7 meals/week (0)	- 0.078 ± 0.033 0.077 ± 0.039 0.253 ± 0.231 0.296 ± 0.298 0.270 ± 0.251 0.537 ± 0.223 -
							[Visit 4]	
							0 meals/past 3 months (0) 1 meal/ past 3 months (3) 1 meal/month (15) 2-3 meals/month (30) 1 meal/week (28) 2-3 meals/week (25) 4-6 meals/week (0) ≥ 7 meals/week (0)	- 0.062 ± 0.026 0.237 ± 0.305 0.182 ± 0.249 0.309 ± 0.392 0.292 ± 0.237 - -
							[Visit 5]	
							0 meals/past 3 months (0) 1 meal/ past 3 months (3) 1 meal/month (21) 2-3 meals/month (49) 1 meal/week (30) 2-3 meals/week (18) 4-6 meals/week (0) ≥ 7 meals/week (2)	- 0.113 ± 0.114 0.141 ± 0.163 0.186 ± 0.236 0.220 ± 0.147 0.818 ± 1.419 - 0.478 ± 0.039
Dong *et al.* (2015) [b] [170]								
					Median (Range)			***[Mean ± SD (µg/g)]***
CS	USA	FCF Question(s) on a Multipurpose Questionnaire	TDA-AAS	153	51 (3-35)	F (80) M (73)	0 meals/week (45) 1-2 meals/week (65) 2-9 meals/week (30)	0.23 ± 0.19 0.48 ± 0.44 0.75 ± 0.64

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Hair**
Masih *et al.* (2016) [171]								
					Cat (n)			***[Mean (µg/g)]***
CS	India	FCF Question(s) on a Multipurpose Questionnaire	AAS	111	2-5 (14) 6-15 (21) 16-49 (45) ≥ 50 (31)		1 meal/6 months (17) 1 meal/2 months (21) ≥ 1 meal/month (31) ≥ 1 meal/week (40)	0.03 0.04 0.06 0.15
						F (53)	1 meal/6 months (8) 1 meal/2 months (11) ≥ 1 meal/month (15) ≥ 1 meal/week (19)	0.01 0.02 0.03 0.06
						M (58)	1 meal/6 months (9) 1 meal/2 months (12) ≥ 1 meal/month (16) ≥ 1 meal/week (21)	0.02 0.02 0.03 0.06

Study Design: CS = Cross-Sectional; PC = Prospective Cohort; SCS = Series Cross-Sectional; CC=Case-Control; RC = Retrospective Cohort
Fish Intake Measurement Method: FCF = Fish Consumption Frequency; FFQ = Food Frequency Questionnaire
Lab Test Method: CV-AAS = Cold Vapor Atomic Absorption Spectrometry; AAS = Atomic Absorption Spectrometry; AA = Atomic Absorption; CGA-AAS = Combustion Gold Amalgamation Atomic Absorption Spectrometry; GC = Gas Chromatography; ICP-MS = Inductively Coupled Plasma Mass Spectrometry; HV-AFS = Hydride Vapor Atomic Fluorescence Spectrometry; CV-AFS = Cold Vapor Atomic Fluorescence Spectrometry; GF-AAS = Graphite Furnace Atomic Absorption Spectrophotometry; DMA = Direct Mercury Analyzer; OC-GA = Oxygen Combustion Gold Amalgamation; TD-AAS = Thermal Decomposition Atomic Absorption Spectrophotometry
Sex: M = Male; F = Female

Table 3: *Methylmercury concentrations measured in hair, stratified by fish consumption frequency*

Study Characteristics					Demographic Characteristics		Concentrations of Methylmercury in Hair Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**MeHg in Hair**
Chen *et al.* (1990) [117]								
					[Mean]		***Permanently Waved [Husbands]***	***[Mean ± SD (µg/g)]***
CS	Japan	FCF Question(s) on a Multipurpose Questionnaire	GC	106	42	F (53) M (53)	≤ 6 meals/week (37) ≥ 7 meals/week (13)	2.61 ± 0.993 3.95 ± 1.783
							[Wives]	
							≤ 6 meals/week (37) ≥ 7 meals/week (13)	1.38 ± 0.157 2.09 ± 0.878
							Not Permanently Waved [Husbands]	
							≤ 6 meals/week (13) ≥ 7 meals/week (6)	2.69 ± 1.479 4.01 ± 1.972
							[Wives]	
							≤ 6 meals/week (13) ≥ 7 meals/week (6)	1.63 ± 0.681 1.92 ± 0.626
Shao *et al.* (2013) [156]								
					[Mean]			***[Mean ± SD (µg/g)]***
CS	China	FCF Question(s) on a Multipurpose Questionnaire	Modular Mercury System	91	33.4	No Data	0-1 meals/week (23) 2-4 meals/week (37) > 4 meals/week (40)	0.34 ± 0.23 0.41 ± 0.37 0.90 ± 0.78

Study Design: CS = Cross-Sectional
Fish Intake Measurement Method: FCF = Fish Consumption Frequency
Lab Test Method: GC = Gas Chromatography
Sex: M = Male; F = Female

Table 4: *Total mercury measured in blood, stratified by fish consumption frequency*

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Blood Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Blood**
Grandjean *et al.* (1992) [118]								
					[Range]			***[Median (50% Range) nmol/L]***
CS	Faroe Islands (Norway)	FCF Question(s) on a Multipurpose Questionnaire	AA	997	20-50	F	0 meals/week (27) 1 meal/week (141) 2 meals/week (365) 3 meals/week (295) 4 meals/week (158) ≥ 5 meals/week (33)	35.6 (13.2-101) 93.7 (37.9-163) 112 (66.4-186) 134 (65.1-220) 146 (94.2-210) 169 (89.5-240)
Weihe *et al.* (1996) [123]								
					[Range]		***[Whale Consumption]***	***[Median (50% Range) nmol/L]***
CS	Faroe Islands (Norway)	FCF Question(s) on a Multipurpose Questionnaire	AA	997	20-50	F	0 meals/month (204) 1 meal/month (277) 2 meals/month (243) 3 meals/month (86) ≥ 4 meals/month (180)	53.3 (29.9-94.6) 96.2 (60.6-159) 142 (80.8-217) 207 (139-298) 180 (122-300)
Oskarsson *et al.* (1996) [172]								
		FCF Question(s)			***[Mean ± SD]***			***[Mean ± SD (ng/g)]***
CS	Sweden	on a Multipurpose Questionnaire	CV-AAS	30	30 ± 6	F	0 meals/6 weeks (24) 1-2 meals/6 weeks (6)	2.0 ± 0.8 3.5 ± 0.7
Kosatsky *et al.* (2000) [129]								
					[Mean ± SD]			***[Geometric Mean ± SD (µg/L)]***
CS	Canada	Fish-Focused FFQ	CV-AAS	132	46.7 ± 14	F (15) M (117)	***[Overall]*** < 1 meal/week (72) ≥ 1 meal/week (60)	1.44 ± 2.23 3.03 ± 2.43
							[Perch]	***[Geometric Mean (95%CI) (µg/L)]***
							< 1 meal/week (56) ≥ 1 meal/week (57)	1.75 (1.46, 2.09) 2.92 (2.16, 3.95)
							[Pike] < 1 meal/week (18) ≥ 1 meal/week (25)	 1.92 (1.64, 2.25) 5.59 (2.26, 13.8)
							[Walleye] < 1 meal/week (30) ≥ 1 meal/week (36)	 1.95 (1.66, 2.3) 2.78 (1.49, 5.21)

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Blood Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Blood**
Kim *et al.* (2006) [173]								
CS	Peru	FCF Question(s) on a Multipurpose Questionnaire	Mercury Analyzer	103	***[Range]*** 24-40	F		***[Median (Range) (µg/L)]***
							0 meals/month (7)	2.79 (1.05-4.78)
							1 meal/month (11)	1.3 (0.4-10.75)
							2 meals/month (12)	2.31 (0.14-4.29)
							4 meals/month (24)	2.58 (0.25-5.7)
							≥ 12 meals/month (9)	4.71 (1.86-10.45)
Bates *et al.* (2007) [174]								
CS	England	Weighed Dietary Records (7 Days)	ICP-MS	1,318	***Cat (n)*** 19-24 (80)	F (660) M (550)	***[Consumption Scores ∞] [Total Fish]***	***[Geometric Mean (nmol/L)***
							1 (344)	2.97
					25-34 (249)		2 (284)	5.49
							3 (300)	6.8
					35-49 (490)		4 (288)	9.76
							[Fried White Fish]	
					50-64 (373)		1 (800)	5.44
							2 (145)	5.14
							3 (131)	6.53
							4 (140)	6.01
							[Other White Fish]	
							1 (1000)	5.05
							2 (71)	9.71
							3 (72)	7.34
							4 (73)	9.66
							[Shellfish]	
							1 (988)	5.02
							2 (75)	7.36
							3 (77)	8.67
							4 (76)	10.73
							[Oily Fish]	
							1 (665)	3.79
							2 (194)	6.99
							3 (176)	9.05
							4 (181)	11.4

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Blood Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Blood**
McKelvey *et al.* (2007) [175]								
CS	USA	General FFQ (30 Day Period)	ICP-MS	1,811	***Cat (n)*** 20-39 (903) 40-59 (673) ≥ 60 (235)			***[Geometric Mean (95%CI) (µg/dL)]***
							0 meals/30 days (209)	1.31 (1.14, 1.5)
							1-9 meals/30 days (1,216)	2.60 (2.46, 2.74)
							10-19 meals/30 days (255)	4.25 (3.79, 4.76)
							≥ 20 meals/30 days (114)	5.65 (4.80, 6.65)
Marques *et al.* (2007) [134]								
CS	Brazil	FCF Question(s) on a Multipurpose Questionnaire	CV-AAS	100	***[Range]*** 15-40	F		***[Median (Range) (µg/L)]***
							0-1 meals/week (57)	0.6 (0.01-10)
							≥ 2 meals/week (43)	0.5 (0.01-10)
Smith *et al.* (2009) [176]								
SCS	USA	General FFQ (30 Day Period)	CV-AFS	1,726	***Mean ± SE*** 32.1 ± 2.5	F		***[Mean ± SE (µg/L)]***
							Non-consumers (441)	0.6 ± 0.05
							1-4 meals/30 days (616)	1.6 ± 0.1
							5-8 meals/30 days (131)	2.2 ± 0.3
							≥ 9 meals/30 days (57)	4.2 ± 0.7
Puklova *et al.* (2010) [142]								
PC	Czech Republic	General FFQ	AAS	411		F (163) M (248)		***[Median (µg/L)]***
							Never	0.51
							< 1 meal/week	0.81
							≥ 1 meal/week	0.95
Gibb *et al.* (2011) [177]								
CS	Ukraine *Artemivsk*	FCF Question(s) on a Multipurpose Questionnaire	ICP-MS	61	***[Range]*** 16-71			***[Median (µg/L)]***
						F (26) M (4)	< 1 meal/week (13) ≥ 1 meal/week (17)	0.92 0.9
	Horlivka					F (28) M (3)	< 1 meal/week (13) ≥ 1 meal/week (17)	1.2 0.89

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Blood Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Blood**
Sadagoparamanujama *et al.* (2011) [178]								
							[All Fish]	***[Mean ± SD (µg/L)]***
CS	USA	FCF Question(s) on a Multipurpose Questionnaire	CV-AAS	175		F	0 meals/week	4.7 ± 5.2
							1 meal/week	6.21 ± 1.9
							2 meals/week	14.3 ± 9.6
							≥ 3 meals/week	39.2 ± 21.6
							[Tuna]	
							0 meals/week	17.4 ± 15.7
							1 meal/week	26.6 ± 16.3
							2 meals/week	41.1 ± 25.7
							≥ 3 meals/week	58.8 ± 24.1
							[Shrimp]	
							0 meals/week	20.9 ± 19.8
							1 meal/week	25.8 ± 16.3
							2 meals/week	37.9 ± 13.1
							≥ 3 meals/week	69.1 ± 26.4
							[Catfish]	
							0 meals/week	20.8 ± 17.6
							1 meal/week	37.3 ± 25.1
							2 meals/week	41.2 ± 16.2
							≥ 3 meals/week	69.5 ± 27.3
							[Oysters]	
							0 meals/week	24.7 ± 19.7
							1 meal/week	39.3 ± 20.7
							2 meals/week	50.2 ± 25.1
							≥ 3 meals/week	56.2 ± 38.4

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Blood Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Blood**
Sadagoparamanujama *et al.* (2011) *(Continued)* [178]								
CS	*USA*	*FCF Question(s) on a Multipurpose Questionnaire*	*CV-AAS*	*175*		*F*	***[Crab]***	***[Mean ± SD (µg/L)]***
							0 meals/week	25.1 ± 20.6
							1 meal/week	39.6 ± 25.4
							2 meals/week	44.4 ± 17.3
							≥ 3 meals/week	55.5 ± 31.2
							[Other Fish]	
							0 meals/week	20.3 ± 18.5
							1 meal/week	23.6 ± 14.1
							2 meals/week	46.3 ± 24.1
							≥ 3 meals/week	47.1 ± 22.6
Gump *et al.* (2012) [179]								
CS	USA	General FFQ	ICP-MS	100	***[Range]***			***[Mean (µg/L)]***
					9-11	F (43)	Doesn't eat fish (45)	0.41
						M (57)	Eats fish (50)	1.11
Tsuji *et al.* (2012) [180]								
CS	Japan	Fish-Focused FFQ	CV-AAS	269	No Data	F (171)		***[Geometric Mean (95%CI) (ng/L)]***
							< 2 meals/week (21)	22.1 (15.9, 30.7)
							3-4 meals/week (79)	25.2 (21.2, 30.1)
							5-6 meals/week (45)	24.1 (19.5, 29.7)
							≥ 7 meals/week (20)	35.1 (26.1, 47.2)
						M (98)	< 2 meals/week (14)	50.1 (35, 71.7)
							3-4 meals/week (34)	41.7 (32.2, 53.8)
							5-6 meals/week (23)	35.7 (26.5, 48.3)
							≥ 7 meals/week (21)	51.9 (38.1, 70.8)
Yard *et al.* (2012) [181]								
CS	Peru	FCF Question(s) on a Multipurpose Questionnaire	HP-LC	103	***[Range]***			***[Geometric Mean (µg/L)]***
					3-70	F (46)	Doesn't eat fish (35)	1.61
						M (55)	Eats fish (50)	2.58
Birgisdottir *et al.* (2013) [182]								
CS	Norway	General FFQ	ICP-MS	179	***Cat (n)***	F (98)	≤ 34 g/day (61)	***[Median (µg/L)]***
					< 40 (33)	M (81)	34-65 g/day (60)	2.4
					40-60 (73)		>65 g/day (58)	4.5
					> 60 (73)			6.5

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Blood Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Blood**
Garcia-Esquinas *et al.* (2013) *§* [183]								
CS	Spain	General FFQ	CV-AAS	114	No Data	No Data	***[Maternal Consumption]*** ≤ 60 g/day (38) 61-100 g/day (34) >100 g/day (34)	***[Geometric Mean (95%CI) (µg/L)]*** 5.18 (4.03, 6.66) 7.12 (4.96, 10.2) 8.54 (6.99, 10.4)
Karimi *et al.* (2014) [184]								
CS	USA	Semi-Quantitative Block FFQ	ICP-MS	285	***Cat (n)*** 18-39 (95) 40-59 (105) ≥ 60 (95)	F (166) M (119)	A few meals/year (6) 1 meal/month (5) 2-3 meals/month (17) 1 meal/week (31) 2 meals/week (68) 3-4 meals/week (105) 5-6 meals/week (35) 1 meal/day (7)	***[Geometric Mean (µg/L)]*** 2.83 1.91 2.41 3.17 3.05 5.94 7.67 17.03
Buscemi *et al.* (2014) [185]								
CS	Italy	Semi-Quantitative FFQ (Past 12 Months)	ICP-MS	54	***Mean ± SD*** 50.6 ± 11.9	F (34) M (20)	< 1 meal/week (19) ≥ 3 meals/week (24)	***[Mean ± SD (µg/L)]*** 1.65 ± 1.09 5.87 ± 2.69
Prokopowicz *et al.* (2014) [186]								
CS	Poland	FCF Question(s) on General Questionnaire	CV-AAS	80	***Mean ± SD*** 55.5 ± 2.7	F	0-1 meals/month 2-6 meals/month 7 to 20 meals/month	***[Geometric Mean (95%CI) (µg/L)]*** 0.36 (0.14, 0.94) 0.72 (0.61, 0.85) 1.19 (0.67, 2.12)
Kim *et al.* (2014) [187]								
CS	South Korea	General FFQ	DMA 80	3,397	***Cat (n)*** 20-29 (775) 30-39 (795) 40-49 (800) 50-59 (790) ≥ 60 (812)	F (1,978) M (1,994)	***[Mackerel (Total)]*** Rare (633) ≤ 1 meal/month (653) 2-4 meals/month (1,582) ≥ 1 meal/week (402) ***[Mackerel (F)]*** Rare (354) ≤ 1 meal/month (337) 2-4 meals/month (823) ≥ 1 meal/week (208)	***[Mean ± SE (µg/L)]*** 4.73 ± 0.20 5.07 ± 0.16 5.55 ± 0.12 6.13 ± 0.31 3.92 ± 0.16 4.23 ± 0.18 4.20 ± 0.10 4.67 ± 0.16

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Blood Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Blood**
Kim *et al.* (2014) *(Continued)* [187]								
					Cat (n)		***[Mackerel (M)]***	***[Mean ± SE (µg/L)]***
CS	*South Korea*	*General FFQ*	*DMA 80*	*3,397*	*20-29 (775)* *30-39 (795)* *40-49 (800)* *50-59 (790)* *≥ 60 (812)*	*F (1,978)* *M (1,994)*	Rare (279)	5.45 ± 0.34
							≤ 1 meal/month (316)	5.79 ± 0.26
							2-4 meals/month (759)	6.59 ± 0.19
							≥ 1 meal/week (194)	7.39 ± 0.54
							[Tuna (Total)]	
							Rare (1,474)	5.45 ± 0.15
							≤ 1 meal/month (587)	5.37 ± 0.19
							2-4 meals/month (1,012)	5.20 ± 0.12
							≥ 1 meal/week (197)	5.94 ± 0.41
							[Tuna (F)]	
							Rare (795)	4.33 ± 0.10
							≤ 1 meal/month (288)	4.40 ± 0.20
							2-4 meals/month (536)	4.05 ± 0.11
							≥ 1 meal/week (103)	4.58 ± 0.26
							[Tuna (M)]	
							Rare (679)	6.52 ± 6.26
							≤ 1 meal/month (299)	6.05 ± 0.28
							2-4 meals/month (476)	6.15 ± 0.21
							≥ 1 meal/week (94)	7.09 ± 0.66
							[Yellow Corvina (Total)]	
							Rare (1,079)	4.89 ± 0.13
							≤ 1 meal/month (768)	5.53 ± 0.20
							2-4 meals/month (1,161)	5.64 ± 0.14
							≥ 1 meal/week (262)	5.94 ± 0.30
							[Yellow Corvina (F)]	
							Rare (551)	3.93 ± 0.11
							≤ 1 meal/month (385)	4.19 ± 0.14
							2-4 meals/month (642)	4.52 ± 0.13
							≥ 1 meal/week (144)	4.64 ± 0.24
							[Yellow Corvina (M)]	
							Rare (528)	5.65 ± 0.21
							≤ 1 meal/month (383)	6.53 ± 0.32
							2-4 meals/month (519)	6.71 ± 0.23
							≥ 1 meal/week (118)	7.30 ± 0.52

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Blood Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Blood**
Kim *et al.* (2014) *(Continued)* [187]								
					Cat (n)		***[Squid (Total)]***	***[Mean ± SE (µg/L)]***
CS	*South Korea*	*General FFQ*	*DMA 80*	*3,397*	*20-29 (775)*	*F (1,978)*	Rare (1,189)	5.25 ± 0.14
						M (1,994)	≤ 1 meal/month (754)	5.42 ± 0.17
					30-39 (795)		2-4 meals/month (1,072)	5.31 ± 0.13
							≥ 1 meal/week (255)	5.98 ± 0.38
					40-49 (800)		***[Squid (F)]***	
							Rare (646)	4.14 ± 0.11
					50-59 (790)		≤ 1 meal/month (405)	4.07 ± 0.13
							2-4 meals/month (548)	4.37 ± 0.14
					≥ 60 (812)		≥ 1 meal/week (123)	4.86 ± 0.27
							[Squid (M)]	
							Rare (543)	6.30 ± 0.25
							≤ 1 meal/month (349)	6.61 ± 0.31
							2-4 meals/month (524)	6.06 ± 0.20
							≥ 1 meal/week (132)	6.81 ± 0.62
							[Clam (Total)]	
							Rare (1,231)	4.92 ± 0.13
							≤ 1 meal/month (777)	5.73 ± 0.23
							2-4 meals/month (1,043)	5.49 ± 0.13
							≥ 1 meal/week (219)	5.88 ± 0.28
							[Clam (F)]	
							Rare (707)	4.00 ± 0.11
							≤ 1 meal/month (373)	4.37 ± 0.15
							2-4 meals/month (523)	4.26 ± 0.10
							≥ 1 meal/week (119)	5.33 ± 0.40
							[Clam (M)]	
							Rare (524)	5.90 ± 0.23
							≤ 1 meal/month (404)	6.69 ± 0.38
							2-4 meals/month (520)	6.43 ± 0.20
							≥ 1 meal/week (100)	6.40 ± 0.37

Study Design: CS = Cross-Sectional; PC = Prospective Cohort
Fish Intake Measurement Method: FCF = Fish Consumption Frequency; FFQ = Food Frequency Questionnaire
Lab Test Method: CV-AAS = Cold Vapor Atomic Absorption Spectrometry; AAS = Atomic Absorption Spectrometry; AA = Atomic Absorption; CV-AFS = Cold Vapour Atomic Fluorescence Spectrometry; DMA = Direct Mercury Analyzer; HP-LC = High Performance Liquid Chromatography
Sex: M = Male; F = Female; § Cord blood; ∞ = Consumption score of 1 corresponds to 0 intake in 7 days, and scores of 2, 3 or 4 correspond to ascending 3rds of intake measured in grams

Table 5: *Methylmercury concentrations measured in blood, stratified by fish consumption frequency*

Study Characteristics					Demographic Characteristics		Concentrations of Methylmercury in Blood Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**MeHg in Blood**
Schober *et al.* (2003) [114]								
SCS	USA	24-Hour Recall & General FFQ (Past 30 Days)	CV-AFS	705	***[Range]*** 1-5	F M	***[Fish Consumption]***	***[Geometric Mean (95%CI) (µg/L)]***
							0 meals/30 days (285)	0.24 (0.21, 0.27)
							≥ 1 meal/30 days (382)	0.44 (0.35, 0.53)
							[Shellfish Consumption]	
							0 meals/30 days (487)	0.32 (0.27, 0.37)
							≥ 1 meal/30 days (179)	0.45 (0.32, 0.58)
				1709	16-49	F	***[Fish Consumption]***	
							0 meals/30 days (630)	0.51 (0.43, 0.59)
							1-2 meals/30 days (565)	1.05 (0.84, 1.26)
							≥ 3 meals/30 days (448)	1.94 (1.52, 2.35)
							[Shellfish Consumption]	
							0 meals/30 days (868)	0.69 (0.57, 0.81)
							1-2 meals/30 days (468)	1.08 (0.90, 1.25
							≥ 3 meals/30 days (308)	2.10 (1.66, 2.54)
Mahaffey *et al.* (2004) [113]								
SCS	USA	24-Hour Recall & General FFQ (Past 30 Days)	CV-AFS	1727	***[Cat(n)]*** 16-19 (523) 20-29 (448) 30-39 (402) 40-49 (362)	F	***[Fish Consumption]***	***[Geometric Mean (95%CI) (µg/L)]***
							0 meals/30 days (729)	0.43 (0.37, 0.49)
							1-4 meals/30 days (733)	0.93 (0.76, 1.11)
							5-8 meals/30 days (118)	2.04 (1.44, 2.63)
							≥ 9 meals/30 days (63)	2.70 (1.51, 3.89)
							[Fish and Shellfish]	
							0 meals/30 days (480)	0.39 (0.34, 0.44)
							1-4 meals/30 days (780)	0.70 (0.59, 0.82)
							5-8 meals/30 days (118)	1.33 (1.05, 1.60)
							≥ 9 meals/30 days (63)	2.46 (1.82, 3.11)
Bjornberg *et al.* (2005) [131]								
CS	Sweden	General FFQ (Past Year)	CV-AAS	127	***[Range]*** 19-45	F		***[Median (Range) (µg/L)]***
							0 meals/week (26)	1.5 (0.5-4)
							0.1-1 meals/week (87)	1.6 (0.30-10)
							>1 meals/week (13)	3.9 (0.5-14)

Study Characteristics					Demographic Characteristics		Concentrations of Methylmercury in Blood Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**MeHg in Blood**
You *et al.* (2012) [188]								
CS	South Korea	FCF Question(s) on a Multipurpose Questionnaire	CV-AFS	400	***Cat (n)*** 20-29 (60) 30-39 (61) 40-49 (60) 50-59 (102) ≥ 60 (117)	F (200) M (200)	***[Mackerel]*** None (80) < 1 meal/week (242) ≥ 1 meal/week (77) ***[Canned Tuna]*** None (215) < 1 meal/week (150) ≥ 1 meal/week (34) ***[Anchovy]*** None (41) < 1 meal/week (175) ≥ 1 meal/week (183) ***[Tuna]*** None (310) < 1 meal/week (74) ≥ 1 meal/week (15) ***[Mackerel Pike]*** None (240) < 1 meal/week (134) ≥ 1 meal/week (25) ***[Yellow Corvina]*** None (115) < 1 meal/week (218) ≥ 1 meal/week (66) ***[Alaska Pollack]*** None (164) < 1 meal/week (203) ≥ 1 meal/week (32) ***[Sea Bream]*** None (321) < 1 meal/week (71) ≥ 1 meal/week (7)	***[Geometric Mean (95%CI) (µg/L)]*** 3.26 (2.74, 3.87) 4.12 (3.83, 4.44) 4.79 (4.15, 5.54) 4.06 (3.70, 4.45) 4.08 (3.71, 4.50) 3.80 (3.08, 4.70) 3.46 (2.62, 4.56) 3.91 (3.58, 4.27) 4.33 (3.95, 4.75) 3.93 (3.65, 4.23) 4.52 (3.96, 5.17) 4.24 (3.13, 5.73) 3.87 (3.56, 4.21) 4.10 (3.72, 4.53) 5.74 (4.23, 7.78) 3.66 (3.22, 4.17) 4.21 (3.87, 4.57) 4.24 (3.66, 4.90) 3.57 (3.20-3.98) 4.34 (4.00, 4.70) 4.98 (3.99, 6.21) 3.84 (3.57, 4.12) 5.07 (4.44, 5.80) 4.76 (2.31, 9.79)

Study Characteristics					Demographic Characteristics		Concentrations of Methylmercury in Blood Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**MeHg in Blood**
You *et al.* (2012) *(Continued)* [188]								
					Cat (n)			***[Geometric Mean (95%CI) (µg/L)]***
CS	*South Korea*	*FCF Question(s) on a Multipurpose Questionnaire*	*CV-AFS*	*400*	*20-29 (60)* *30-39 (61)* *40-49 (60)* *50-59 (102)* *≥ 60 (117)*	*F (200)* *M (200)*	***[Flatfish]***	
							None (220)	3.53 (3.24, 3.86)
							< 1 meal/week (159)	4.85 (1.16, 5.30)
							≥ 1 meal/week (20)	4.28 (3.10, 5.90)
							[Hair Tail]	
							None (79)	3.12 (2.67, 3.65)
							< 1 meal/week (244)	4.16 (3.86, 4.48)
							≥ 1 meal/week (76)	4.85 (4.16, 5.65)
							[Sushi]	
							None (81)	3.18 (2.71, 3.73)
							< 1 meal/week (251)	4.03 (3.74, 4.33)
							≥ 1 meal/week (67)	5.51 (4.72, 6.43)
							[Pickled Fish]	
							None (175)	3.81 (3.44, 4.21)
							< 1 meal/week (164)	4.15 (3.77, 4.57)
							≥ 1 meal/week (60)	4.52 (3.86, 5.28)
							[Laver]	
							None (36)	3.62 (2.82, 4.65)
							< 1 meal/week (158)	3.82 (3.45, 4.23)
							≥ 1 meal/week (205)	4.31 (3.96, 4.70)
							[Sea Mustard]	
							None (37)	2.89 (2.34, 3.58)
							< 1 meal/week (202)	4.0 (3.67, 4.37)
							≥ 1 meal/week (160)	4.44 (4.01, 4.91)

Study Design: CS = Cross-Sectional; SCS = Series Cross-Sectional
Fish Intake Measurement Method: FCF = Fish Consumption Frequency; FFQ = Food Frequency Questionnaire
Lab Test Method: CV-AAS = Cold Vapor Atomic Absorption Spectrometry; CV-AFS = Cold Vapor Atomic Fluorescence Spectrometry
Sex: M = Male; F = Female

Table 6: *Total mercury concentrations measured in urine, stratified by fish consumption frequency*

Study Characteristics					Demographic Characteristics		Concentrations of Total Mercury in Urine Stratified by Fish Consumption Frequency	
Study Design	**Study Location**	**Fish Intake Measurement Method**	**Lab Test Method**	**n**	**Age (years)**	**Sex Cat (n)**	**Fish Consumption [Frequency (n)]**	**THg in Urine**
Gibb *et al.* (2011) [177]								
					[Range]			***[Median (µg/g C)]***
CS	Ukraine *Artemivsk*	FCF Question(s) on a Multipurpose Questionnaire	ICP-MS	61	16-71	F (26) M (4)	< 1 meal/week (13) ≥ 1 meal/week (17)	0.24 0.29
	Horlivka					F (28) M (3)	< 1 meal/week (13) ≥ 1 meal/week (17)	0.18 0.14
McKelvey *et al.* (2011) [189]								
					[Cat (n)]			***[Geometric Mean (95%CI) (µg/L)]***
CS	USA	General FFQ (Past 30 Days)	ICP-MS	1,840	20-29 (490) 30-39 (425) 40-49 (404) 50-59 (283) ≥ 60 (238)	F (1,074) M (766)	***[Fish and Shellfish]*** Never (215) 1-9 meals/30 days (1,233) 10-19 meals/30 days (258) ≥ 20 meals/30 days (116)	0.50 (0.41, 0.61) 0.71 (0.66, 0.77) 0.92 (0.79, 1.07) 1.02 (0.83, 1.25)
							[(µg/g C)] Never (214) 1-9 meals/30 days (1,221) 10-19 meals/30 days (255) ≥ 20 meals/30 days (116)	 0.44 (0.36, 0.54) 0.68 (0.63, 0.73) 0.83 (0.71, 0.97) 1.03 (0.85, 1.23)
Yard *et al.* (2012) [181]								
					[Range]			***[Geometric Mean (µg/g C)]***
CS	Peru	FCF Question(s) on a Multipurpose Questionnaire	ICP-MS	103	3-70	F (46) M (55)	Doesn't eat fish (35) Eats fish (50)	5.22 6.04
Birgisdottir *et al.* (2013) [182]								
					[Cat (n)]			***[Median (µg/g C)]***
CS	Norway	General FFQ	ICP-MS	179	< 40 (33) 40-60 (73) > 60 (73)	F (98) M (81)	≤ 34 g/day (61) 34-65 g/day (60) >65 g/day (58)	0.88 1 1.2

Study Design: CS = Cross-Sectional
Fish Intake Measurement Method: FCF = Fish Consumption Frequency; FFQ = Food Frequency Questionnaire
Lab Test Method: CV-AAS = Cold Vapour Atomic Absorption Spectrometry; ICP-MS = Inductively Coupled Plasma Mass Spectrometry
Sex: M = Male; F = Female
THg in Urine: µg/g C = µg/g Creatinine

Seafood Intake Measurement

Seafood intake was predominantly measured using items on a multi-purpose questionnaire that included a question that asked participants to report how often they usually consume fish (this method was used in 55% (48/87) of the reviewed studies) (tables 2-6). A food frequency questionnaire (FFQ) containing items measuring fish and shellfish intake was used in 28.7% (25/87) of the reviewed studies. In a small proportion of studies, seafood consumption was measured by a fish-focused FFQ (4.6%; 4/87). Other methods of measuring fish intake were only used in a small number of studies including 24-hour recalls (2.3%; 2/87) and short-term food diaries or direct observation of dietary intake (5.7%; 5/87).

Species of Fish, Shellfish and Marine Mammals Consumed

The degree to which different species of fish or seafood accumulate MeHg is dependent on a number of factors, most notably size [63]. Similarly, the concentration of other compounds like selenium, known to influence the metabolism of MeHg, also differs across species of fish and seafood [63]. However, the types of fish or seafood consumed by participants were not consistently reported in the reviewed literature. Of the reviewed articles, 33% (29/87) had information on the species of fish or seafood consumed by participants [104–106,109,112,113,119,120,123,126,129,133,146,148,149,158,164,168,169,171–173,178,184,187,188,190,191]. An additional 11 articles had information on broader categories of fish or seafood type, for example marine/freshwater fish, or fish/shellfish [107,108,114,115,125,142,154,161,165,174]. Only 17% (15/87) of the reviewed articles reported fish and seafood consumption frequencies and corresponding biomarker concentrations of mercury stratified by fish or seafood type. Of those, 9 articles presented species-specific consumption frequencies.

There was overlap in the species consumed by participants from different geographic regions. The most commonly mentioned types of fish were: Pike (Canada[129,158], United States[113], Sweden[109,119,131,168], Finland[120], Kazakhstan[148], South Korea[188] and Botswana[104]); Perch ((Canada [129], United States[106,113], Sweden[109,119,131,168], Finland[120]); Mackerel (United States[106,113,149,169], South Korea[173,187,188], Japan[164]); Tuna (United States[113,178,184], Sweden[131], Finland[120], South Korea[173,187,188], Japan[164]); and Catfish (United States[106,113,178,184], Mexico[146], Botswana[104]). The most commonly mentioned types of shellfish were: Crab (United States[149,178,192], South Korea[188], Japan[164]); Shrimp (United States[106,149,178,184,192], Japan[164]);

and Clams (United States [178,192], South Korea[187]). Only 4 studies had participants who regularly consume whale (South Korea[188], Faroe Islands[123], Japan [147,191]).

Regulatory bodies like the U.S Food and Drug Administration, Health Canada and the European Commission have defined a maximum allowable concentration of mercury in commercially sold fish and seafood products, which ranges between 0.5-1.0 µg/g [193–195]. For this reason, the source of the consumed fish or seafood is another important consideration when assessing the likely degree of contamination. Among the reviewed articles, 31% (27/87) provided information on whether the fish or seafood consumed by participants was purchased or obtained through sport or subsistence fishing practices [104–108,112,118,119,123,125,128,129,132,133,140,146,148,149,158,161,162,167,168,171,172,178,190]. Of these, 15 articles reported exclusive consumption of non-commercial fish products [104,105,112,118,123,125,128,133,140,149,158,167,171,172,190]. Of 12 articles that reported consumption of both commercial and non-commercial fish products, 5 had the proportion of total fish from commercial or non-commercial sources, and of these, 4 showed that >50% of fish or seafood was obtained commercially [106–108,119,129,132,146,148,161,162,168,178].

Biomarker Concentrations Measured in Blood

Among the studies included in the review, THg was the most common biomarker of exposure measured (Table 4). Of these studies, 71.4% (15/21) yielded measurements of mercury in blood that increased as total fish consumption frequency increased [118,129,142,172,173,175,176,178,179,181–186]. However, the slope and linearity of these increases cannot be directly compared across studies, given diverse units of measurement and category boundaries for fish consumption frequency. Additionally, the distribution of exposure to mercury through routes other than fish in each population could bias the observed relationship between THg and fish consumption frequency in either direction.

Exposure to mercury through pathways other than fish consumption can be assessed by looking at biomarkers of exposure among individuals who do not consume fish. Of 21 studies in which THg was measured in blood, 8 had subsets of participants who reported not eating fish [118,173–176,178,181,187]. Among these studies, THg concentrations for the non-fish eating categories were as follows: median (µg/L) ranged from 2.79 to 7.14 (7.14 µg/L converted from 35.6 nmol/L using a molecular mass of 200.59) [118,173]; mean (µg/L) ranged from 0.6 to 4.7 [176,178]; and geometric mean µg/L ranged from 0.6 to 13.1 (0.6 µg/L converted from 2.97 nmol/L using a molecular mass of 200.59) [174,175,181,187]. This comparison indicates that levels of mercury exposure from sources other than fish vary substantially across populations

[118,173–176,178,181,187]. The extent to which this variation affects the apparent relationship between THg and fish consumption within each study depends on whether the frequency of exposure to mercury through other pathways is consistent across subsets that consume different quantities of fish.

MeHg concentration in blood was measured in 4 of the reviewed studies (table 5). Consistent increases in blood MeHg levels with increasing frequency of total fish and shellfish consumption were apparent in the 3 studies that estimated this association (table 5) [113,114,131]. Further, in the results presented by Schober *et al.* (2013) [114] and Mahaffey *et al.* (2004) [113], there is little or no overlap in the 95% CIs for the geometric means for each consecutive category of fish consumption, providing stronger evidence of a positive association between these two variables. However, as with results from studies in which THg was the measured biomarker, the strength and shape of the dose-response cannot be directly compared across studies. In the study by You *et al.* (2012), fish consumption frequencies and corresponding MeHg concentrations were stratified further by specific types of fish [196]. In these results, geometric mean levels of MeHg did not increase as consumption increased for some species (table 5) [196].

Among articles included in the review that presented blood mercury concentrations, only 12% (3/25) measured fish consumption using methods that captured intake in the days preceding sample collection [113,114,174]. However, 2 of these studies employed both 24-hour recall and a general FFQ measuring usual intake over the past 30 days and blood mercury concentrations presented in the papers were stratified by fish consumption measured through the FFQ [113,114]. In the remaining studies, fish intake was measured using either fish-focused or general FFQs [118,123,129,134,142,172,173,175–187]. Among studies that specified the reference period for the FFQs, they ranged from the past 30 days to the past 12 months [175,176,185]. Given the potential for variation in time since most recent exposure and in biological responses to mercury exposure within these study populations, the estimated associations between blood mercury concentrations and fish consumption may be biased in either direction.

Biomarker Concentrations Measured in Urine

In the studies conducted by McKelvey *et al.* (2011) [189] and Yard *et al.* (2012) [181] spot urine samples were collected. In the study conducted by Birgisdottir *et al.* (2013) [182], spot samples were collected during the first urination of the day. Gibb *et al.* (2011) [177] did not specify the method used to collect samples. Only one of the reviewed studies included an

assessment of kidney health among participants [181]. In this study, 9 of 103 participants reported having been previously diagnosed with kidney dysfunction by a health care professional [181]. The authors reported an increased concentration of mercury in the urine among participants who reported having kidney dysfunction, relative to those who did not [181]. However, the small sample of participants who reported kidney dysfunction precludes drawing inferences about this trend.

In the study by McKelvey *et al.* (2011), geometric mean concentrations of mercury increased with increasing fish consumption frequency (Table 6) [189]. The authors interpreted this increase as providing evidence against the conventional assumptions about the lack of relationship between mercury in urine and fish consumption [189]. Urine-mercury concentrations measured in the studies by Yard *et al.* (2012) and Birgisdottir *et al.* (2013) also increased slightly with increasing fish consumption frequency (Table 6) [181,182]. However, the authors did not provide estimates of the variance around the geometric mean or median values [181,182]. Without estimates of the variance around values for each category, conclusions cannot be drawn about the extent to which mercury concentrations differ across categories of fish consumption [181,182].

Biomarker Concentrations Measured in Hair

The suitability of hair for measuring exposure to mercury and in particular MeHg is reflected in the number of studies that selected this matrix (77%; 67/87) (Tables 2 and 3). THg was the most common biomarker, being used in 98.5% (67/68) of the studies that measured concentrations in hair (Table 2). There were 26 studies in which a portion of the population reported not consuming any fish [105–108,110,115,118,124,125,128,131,132,136,139,142,144,148,155,159,160,166,168]. Of these, mean values ranged from 0.06 to 0.95 µg/g [105–108,110,115,128,131,136,139,144,148,155,159,160,166,168]; median values ranged from 0.09 to 1.4 µg/g (1.4 µg/g converted from 7.0 nmol/g using a molecular weight of 200.59) [118,132,142]; and geometric mean values ranged from 0.24 to 0.70 µg/g [124,125]. While some variation in background levels across studies exists, the degree of variation is much lower than seen among non-consumers of fish in studies that measured THg in blood. Of studies in which THg was measured in hair, 66% (44/67) yielded estimates of THg in hair that increased consistently as fish consumption increased in the study population.

Meta-Analysis of THg Concentrations Measured in Hair

Analysis of Summary Data

Re-Analysis of Published Data

Of 67 articles reporting THg levels in hair stratified by fish consumption frequency, 13 had sufficient sample sizes and provided estimates of arithmetic mean THg in hair for compatible fish frequency categories, allowing for direct comparison across studies (Table 7). One study was removed because of a small sample size (n=19) and highly imprecise estimates [111]. Each of these studies used a unique dataset. Standard deviations were missing for 3 of the studies included in this analysis (Salehi & Esmaili-Sari (2010) [141], Traynor *et al.* (2013)[155] and Knobeloch *et al.* (2007)[132]). The means of SDs from the remaining studies in the analysis were used in place of the missing values for each exposure category [88,100]. The missing values were also imputed using a worst-case scenario approach, with the highest SDs from each exposure category reported in other included articles being used in place of missing values (data not shown). Results of this comparison indicated that the mean imputation approach did not significantly alter inferences drawn from this analysis. In the article by Olivero-Verbel *et al.* (2011), category-specific sample sizes beyond the < 1 meal/week category (n=0) were not reported [150]. Comparable populations included in the review were used to estimate the distribution of this study population across categories of fish consumption frequency. Populations were deemed comparable based on their geographic location and compatible fish consumption frequency data. Since the study by Olivero-Verbel *et al.* (2011) was conducted in Colombia, other studies conducted in South America were selected. Specifically, data from Kim *et al.* (2006) (Peru)[173], Ashe *et al.* (2012) (Peru)[152], and Cordier *et al.* (1998) (French Guiana)[125] were used. Using the combined sample size for the categories 1-2 meals/week and ≥ 3 meals/week as the denominator, the proportion of each study population in each of these categories was calculated. The mean values estimated from the study-specific proportions were then used as estimates of the distribution of the study population in the study by Oliver-Verbel *et al.* (2011) across categories of fish consumption frequency.

Relationship between Fish Consumption Frequency and Hair-Mercury (µg/g)

The *a priori* criteria for drawing inferences about the presence of a dose-response relationship from categorical summary data was satisfied in 91% (10/11) of the studies with data for all 3 categories of fish consumption frequency (table 7) [91,104,105,110,112,132,149,155,160,161,170]. Of 2 studies without participants in the lowest fish consumption category, only 1 had a mean THg concentration in among consumers of ≥ 3

meals/week that was higher than that of those consuming 1-2 meals/week [141,150]. Figure 7 shows the mean THg values and corresponding 95%CIs for each category of fish consumption from the 13 studies included in the analysis. The shape of the relationship between these variables appears linear among study populations with hair-mercury concentrations below 1 μg/g. Conversely, the shape of this relationship among study populations with higher hair-mercury concentrations appears non-linear and varies across studies. Differences in mean THg and corresponding SEs comparing consecutive levels of fish consumption frequency are shown in table 8. Among studies with data for all 3 categories of fish consumption frequency, only 50% (5/10) had differences in mean THg (μg/g) that remained reasonably consistent across exposure contrasts, suggesting the presence of a linear relationship.

Heterogeneity Across Studies

Results of the multivariate random-effects meta-regression models are shown in table 9. These models yielded evidence of a high level of heterogeneity across studies, particularly for the effect of consuming ≥ 3 vs. 1-2 meals/week on mean μg/g of THg in hair (SD: 1.60; 95%CI: 0.93, 2.28) (table 9). These findings are complemented by the graphs shown in figures 7-11, in which a considerable level of variation in intercepts is evident for both fish consumption frequency contrasts.

The estimated amount of between-study heterogeneity for the effect on mean THg corresponding to the ≥ 3 vs. 1-2 meals/week contrast is greater than that of the 1-2 vs. <1 meal(s)/week. However, the 95% CIs for these SD estimates leave some uncertainty about the extent to which slopes for this effect vary across studies. Visual assessment of the study-specific slopes for the 1-2 vs. <1 meal(s)/week contrast supports the pattern observed in the quantitative estimates. Specifically, while differences in slope are apparent, overlapping 95% CIs around each mean value indicate uncertainty about the degree of beyond-random variation. The particularly high level of heterogeneity in slopes across studies for the ≥3 vs. 1-2 meals/week contrast may be due in part to the highest category being open-ended. If the average number of fish meals/week consumed among participants classified as eating ≥ 3 varied substantially across studies, this could explain some of the heterogeneity in slopes evident in the graphs in figures 7-11.

Study characteristics available for assessment of sources of heterogeneity were geographic location classified by continent (North America, South America, Europe, Africa and Asia), year of data collection, mean age (modeled in years as a continuous variable), and

proportion female. Due to sparse data constraints, only one study-characteristic variable at a time could be included in meta-regression models. With the exception of geographic location, adjustment for single study characteristics did not reduce estimates of heterogeneity across studies for the effect corresponding to either fish intake contrast. The addition of 'continent' as a covariate in the model led to slightly reduced SDs for the study effect corresponding to the 1-2 v. <1 meal(s)/week contrast (SD: 0.62; 95%CI: 0.47, 1.3) and the ≥ 3 vs. 1-2 meals/week contrast (SD: 1.58; 95%CI: 0.87, 2.28). These findings are complemented by the graphs shown in figures 8-11, in which variation across studies with respect to intercept and slope persists following stratification across potential sources of heterogeneity except among graphs stratified by continent. The North American studies included in this analysis were all conducted in the United States. The relationship between fish consumption frequency and hair mercury levels appears reasonably consistent across studies in this subgroup, in the graphs and the multivariate meta-regression results (figure 10). The inclusion of study quality indicators did not partially or completely explain the estimated residual variation across studies (data not shown).

Table 7: *Re-analyzed summary data*

	Study Characteristics				Re-Analyzed Outcome Data		
	Mean Age (Years)	**% Female**	**n**	**Fish Intake Frequency**	**Mean THg (µg/g)**	**SD**	**95% CI**
Al-Majed & Preston (2000) [110]	33.8	0	10	<1 meal/week	0.96	0.15	0.86, 1.05
			25	1-2 meals/week	3.28	1.09	2.85, 3.71
			100	≥ 3 meals/week	4.18	3.22	3.54, 4.82
Elhamri *et al.* (2007) [105]	33.6	37	4	<1 meal/week	0.34	0.07	0.28, 0.41
			65	1-2 meals/week	1.40	0.79	1.21, 1.60
			39	≥ 3 meals/week	6.90	2.86	5.99, 7.81
Knobeloch *et al.* (2007) [132]	49.4	51.8	673	<1 meal/week	0.41	0.41	0.38, 0.44
			1053	1-2 meals/week	0.78	0.87	0.73, 0.83
			301	≥ 3 meals/week	1.15	2.40	0.88, 1.42
Salehi & Esmaili-Sari (2010) [141]	24.4	100	0	<1 meal/week	-	-	-
			67	1-2 meals/week	2.24	0.87	2.03, 2.45
			82	≥ 3 meals/week	4.50	2.40	3.97, 5.03
Lincoln *et al.* (2011) [149]	48.5	10.9	23	<1 meal/week	0.93	0.80	0.58, 1.28
			211	1-2 meals/week	1.10	1.0	0.96, 1.24
			164	≥ 3 meals/week	1.24	1.22	1.05, 1.43
Black *et al.* (2011) [104]	29	59	8	<1 meal/week	0.08	0.04	0.05, 0.11
			60	1-2 meals/week	0.16	0.19	0.11, 0.21
			33	≥ 3 meals/week	0.33	0.26	0.24, 0.42
Olivero-Verbel *et al.* (2011) [150]	33	57	0	<1 meal/week	-	-	-
			746	1-2 meals/week	1.61	0.12	1.60, 1.62
			582	≥ 3 meals/week	1.57	0.30	1.55, 1.59
Okati *et al.* (2012) [153]	26.5	100	27	<1 meal/week	0.96	0.84	0.63, 1.29
			43	1-2 meals/week	3.95	1.74	3.41, 4.49
			23	≥ 3 meals/week	3.55	2.52	2.46, 4.64
Traynor *et al.* (2013) [155]	32.1	100	63	<1 meal/week	0.15	0.41	0.05, 0.25
			292	1-2 meals/week	0.30	0.87	0.20, 0.40
			343	≥ 3 meals/week	0.46	2.40	0.21, 0.71
Schaefer *et al.* (2014) [161]	54	45.9	10	<1 meal/week	0.49	0.29	0.29, 0.70
			50	1-2 meals/week	1.08	1.16	0.75, 1.41
			75	≥ 3 meals/week	1.98	2.26	1.46, 2.50
Michalak *et al.* (2014) [160]	25	64.2	63	<1 meal/week	0.13	0.12	0.10, 0.16
			224	1-2 meals/week	0.20	0.14	0.18, 0.22
			15	≥ 3 meals/week	0.31	0.19	0.20, 0.42
Bonsignore *et al.* (2015) [112]	38.3	52.4	3	<1 meal/week	1.32	0.94	0.18, 2.46
			15	1-2 meals/week	1.97	0.86	1.51, 2.43
			3	≥ 3 meals/week	5.05	0.24	4.77, 5.34
Dong *et al.* (2015) [b] [170]	51	52.3	45	<1 meal/week	0.23	0.19	0.17, 0.29
			65	1-2 meals/week	0.48	0.44	0.37, 0.59
			30	≥ 3 meals/week	0.75	0.64	0.51, 0.99

Table 8: *Differences in mean µg/g total mercury in hair and corresponding SEs*

Author (Publication Date)	1-2 Vs. <1 Fish Meals/Week		≥ 3 Vs. 1-2 Fish Meals/Week	
	Difference in Mean	SE	Difference in Mean	SE
Al-Majed & Preston (2000) [110]	2.32	0.35	0.90	0.65
Elhamri *et al.* (2007) [105]	1.06	0.40	5.50	0.38
Knobeloch *et al.* (2007) [132]	0.37	0.36	0.37	0.09
Salehi & Esmaili-Sari (2010) [141]	-	-	2.26	0.31
Lincoln *et al.* (2011) [149]	0.17	0.22	0.14	0.11
Black *et al.* (2011) [104]	0.08	0.07	0.17	0.05
Olivero-Verbel *et al.* (2011) [150]	-	-	-0.04	0.01
Okati *et al.* (2012) [153]	2.99	0.36	-0.4	0.53
Traynor *et al.* (2013) [155]	0.15	0.11	0.16	0.15
Schaefer *et al.* (2014) [161]	0.59	0.37	0.90	0.35
Michalak *et al.* (2014) [160]	0.07	0.02	0.11	0.04
Bonsignore *et al.* (2015) [112]	0.65	0.55	3.08	0.51
Dong *et al.* (2015) [b] [170]	0.25	0.07	0.27	0.11

Table 9: *Multivariate random-effects meta-regression results*

	Pooled Estimate		Random Effect	
	β	95% CI	SD	95% CI
No Covariates				
Y1	0.77	0.21, 1.33	0.90	0.46, 1.35
Y2	1.04	0.16, 1.92	1.58	0.92, 2.25
Mean Age				
Y1	1.08	0.19, 1.98	0.93	0.46, 1.40
Y2	1.18	-0.20, 2.56	1.66	0.93, 2.38
Continent *				
Y1	1.89	1.10, 2.68	0.61	0.29, 0.93
Y2	1.82	0.27, 3.37	1.55	0.86, 2.25
Proportion Female				
Y1	0.97	-0.37, 2.31	0.95	0.46, 1.45
Y2	1.85	-0.30, 4.01	1.61	0.90, 2.31
Year				
Y1	1.07	0.08, 2.07	0.92	0.44, 1.40
Y2	1.15	-0.36, 2.65	1.66	0.93, 2.39
Age & Continent				
Y1	1.85	1.13, 2.56	0.54	0.22, 0.85
Y2	1.75	0.13, 3.37	1.62	0.86, 2.37
Age, Continent & Proportion Female				
Y1	1.39	0.33, 2.44	0.53	0.21, 0.84
Y2	2.53	-0.51, 5.56	1.67	0.85, 2.39
Age, Continent, Proportion Female & Date				
Y1	1.39	0.27, 2.52	0.56	0.21, 0.92
Y2	2.51	-0.73, 5.75	1.78	0.86, 2.71

Y1: 1-2 Vs. < 1 Fish Meals/Week
Y2: ≥ 3 Vs. 1-2 Fish Meals/Week
***** North America, South America, Europe, Africa and Asia

Figure 7: *Mean total mercury (µg/g) and 95% CIs for each category of fish consumption frequency*

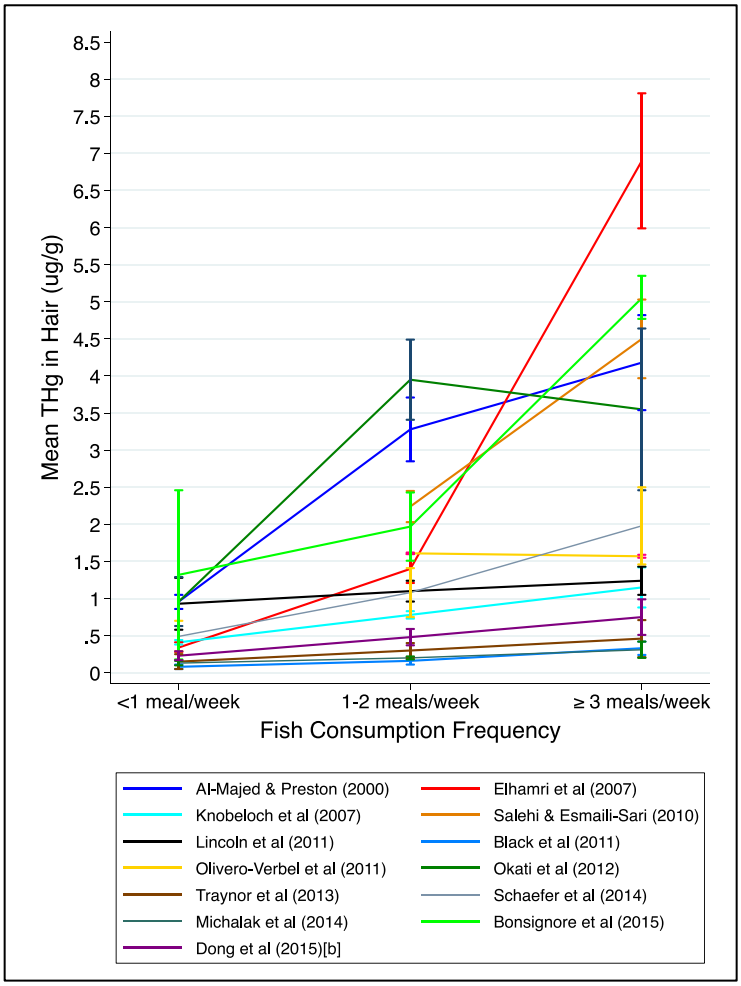


Figure 8: *Mean total mercury (µg/g) and 95% CIs for each category of fish consumption frequency stratified by the proportion of the study population that was male or female*

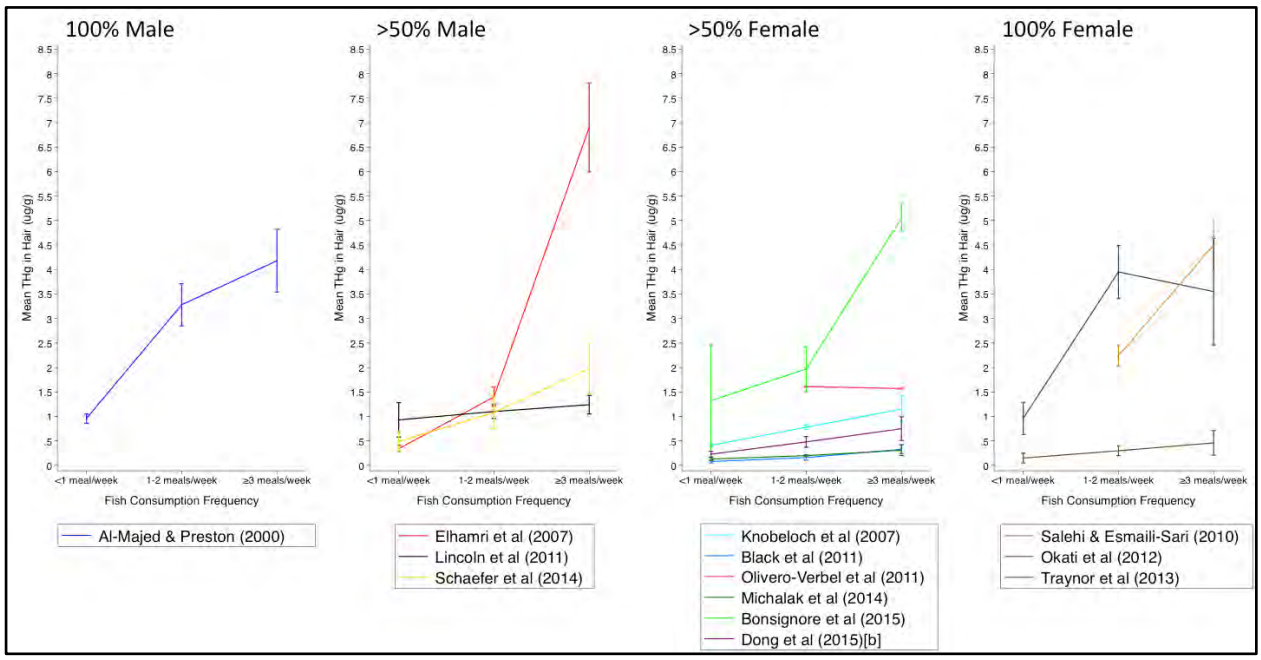


Figure 9: *Mean total mercury (µg/g) and 95% CIs for each category of fish consumption frequency stratified by mean age*

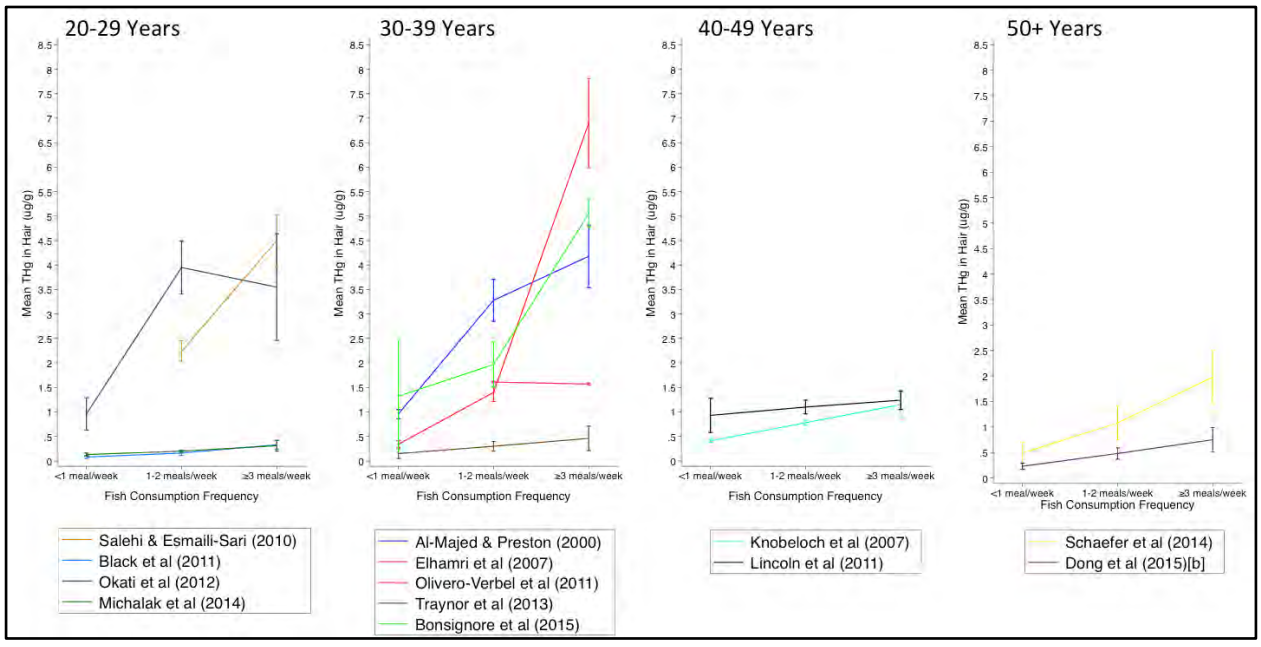


Figure 10: *Mean total mercury (µg/g) and 95% CIs for each category of fish consumption frequency stratified by geographic location*

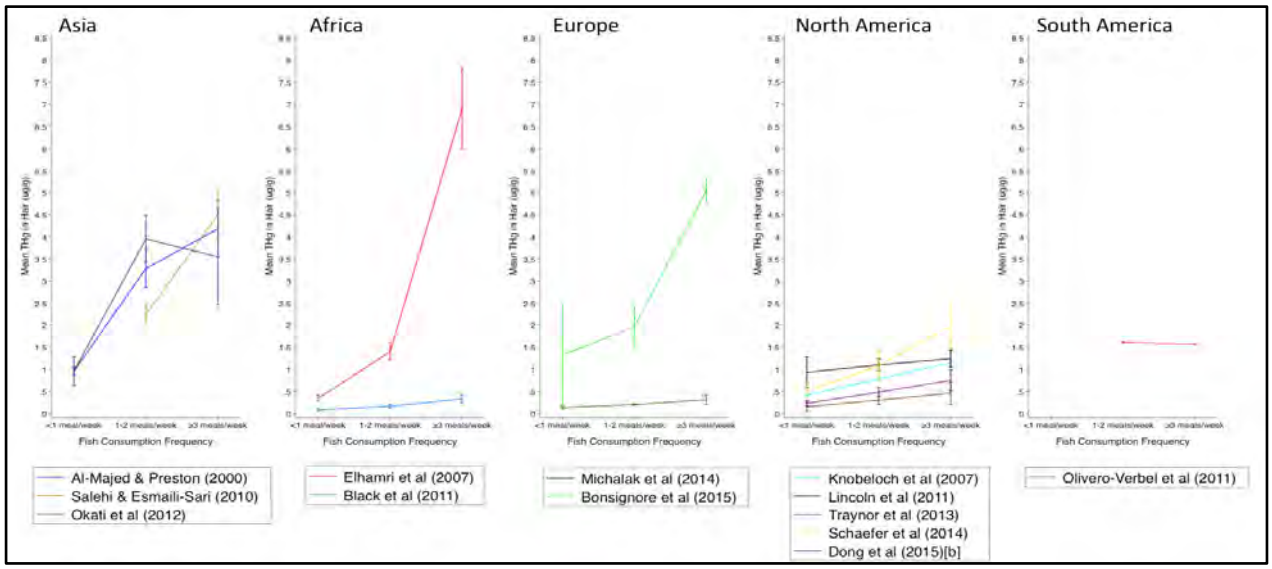
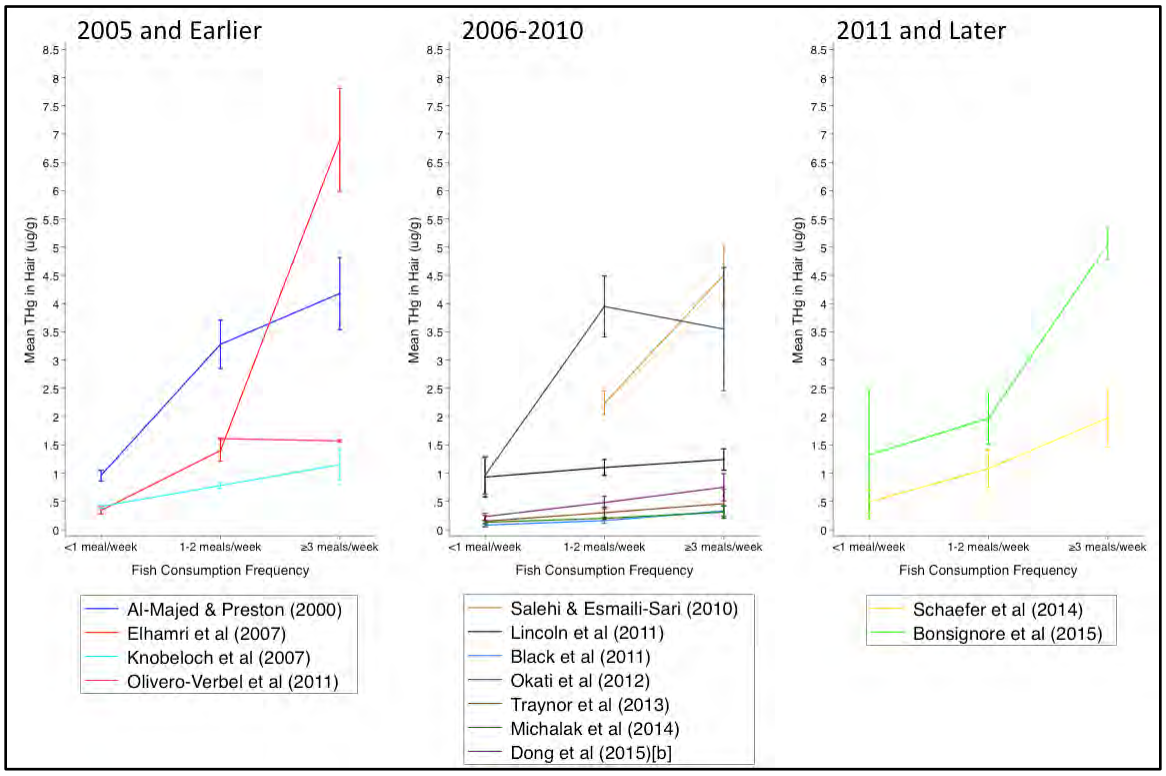


Figure 11: *Mean total mercury (µg/g) and 95% CIs for each category of fish consumption frequency stratified by date of data collection*



Analysis of Pooled Data

Contact information was available for 51 (76%) corresponding authors of reports that presented measurements of mercury in hair. Of the 51 authors contacted, 13 (25%) responded to email requests for the de-identified raw data used to generate the published reports. Datasets were provided by the following authors: Black *et al.* (2011) [104], Elhamri *et al.* (2007) [105], Dong *et al.* (2015) [a] [106], Karouna-Renier *et al.* (2008) [107], Xue *et al.* (2007) [108] and Johnsson *et al.* (2004) [109]. Individual-level data were presented in the published reports by Al-Majed and Preston (2000) [110], Bonsignore *et al.* (2015) [112] and Agah *et al.* (2010) [111].

Study Characteristics

The studies conducted by Black *et al.* (2011) [104], Elhamri *et al.* (2007) [105], Al-Majed and Preston (2000) [110], Agah *et al.* (2010) [111], Bonsignore *et al.* (2015) [112], Johnsson *et al.* (2004) [109], and Karouna-Renier *et al.* (2008) [107] were cross-sectional in design. The study conducted by Xue *et al.* (2007) was prospective with respect to other health outcomes, but hair mercury concentrations and fish consumption frequencies were measured only once at baseline [108]. The study conducted by Dong *et al.* (2015) [a] followed a prospective cohort design. Questionnaire data and hair samples were collected from participants during 5 visits occurring at 3-month intervals [106]. A description of the fish consumption frequency variables from each study for which raw data were available is found in table 10. According to Willett's authoritative nutritional epidemiology text, food items consumed less than once per week are relatively unimportant in terms of overall intake [28]. For this reason, the first analysis of pooled data was restricted to datasets with more detailed response options at higher consumption frequencies (pooled analysis 1). However, given that occasional consumption of a food item with a particularly high concentration of a substance can be important, a second analysis of data from populations with less frequent fish consumption was also conducted (pooled analysis 2) [28].

Table 10: *Descriptions of raw datasets provided by authors of a subset of the included articles*

		Fish Consumption Frequency Variable	
Author (Date)	**n**	**Categorical/ Continuous**	**Categories/Units**
Al-Majed & Preston (2000) [110]	135	Continuous	Number of Fish Meals/Week
Johnsson et al. (2004) [109]	143	Categorical	Never < 1 Fish Meal/Month ≥ 1 Fish Meal/Month, < 1 Fish Meal/Week ≥ 1 Fish Meal/Week
Elhamri *et al.* (2007) [105]	108	Continuous	Number of Fish Meals/Week
Xue et al. (2007) [108]	1,104	Continuous	Number of Fish Meals/Past 6 Months
Karouna-Renier *et al.* (2008) [107]	603	Categorical	None 1 Fish Meal/Past 30 Days 2 Fish Meals/Past 30 Days 3 Fish meals/Past 30 Days > 3 Fish Meals/Past 30 Days
Agah *et al.* (2010) [111]	19	Continuous	Number of Fish Meals/Week
Black *et al.* (2011) [104]	97	Continuous	Number of Fish Meals/Week
Dong *et al.* (2015) [a] [106]	152	Categorical	None 1 Fish Meal/Past 3 Months 1 Fish Meal/Month 2-3 Fish Meals/Month 1 Fish Meal/Week 2-3 Fish Meals/Week 4-6 Fish Meals/Week ≥ 7 Fish Meals/Week
Bonsignore *et al.* (2015) [112]	21	Categorical	Rarely 1-2 Fish Meals/Week ≥ 3 Fish Meals/Week

Pooled Analysis 1

Of the raw datasets provided by authors, 5 had exposure definitions with greater detail at higher consumption frequencies [104–106,108,110]. Baseline measurements for fish consumption frequency and hair mercury concentrations from the cohort study by Dong *et al.* (2015) [a] were combined with data from the other studies for pooled analysis [106]. The rationale for using baseline measurements was predicated on the proportion of the participants who completed all follow-up visits and the consistency of outcome data over time. Specifically, only 51% (77/152) of participants completed all 5 visits. Given the large proportion of participants who missed some follow-up visits, restriction of the study sample to participants who completed all 5 in order to calculate averages across visits may have introduced selection bias [197]. Second, visual inspection of change in THg values across visits for each participant showed that THg levels remained consistent enough to justify including only baseline measurements in the pooled analysis [106].

The distributions of population characteristics and THg concentrations for each study separately and all studies pooled are shown in tables 11 and 12. Summary data are also shown for studies 1-3, as studies conducted by Al-Majed and Preston (2000) [110] and Xue *et al.* (2007) [108] were restricted to either only males or only females. In the studies conducted by Dong *et al.* (2015) [a] [106], Elhamri *et al.* (2007) [105] and Xue *et al.* (2007) [108] hair samples were collected in a manner that permitted root end orientation. The hair samples were trimmed to standardized lengths, to represent the most recent growth period. In the studies by Dong *et al.* (2015) [a] [106] and Elhamri *et al.* (2007) [105], the hair samples were trimmed to 2 cm in length. In the study by Xue *et al.* (2007), pregnant women seeking care at pre-natal clinics in Michigan, U.S., were recruited for participation [108]. In this study, the authors assumed an average growth rate of 1.3 cm/month and trimmed the strand so that the length of each sample corresponded with the length of that participant's pregnancy at the time of data collection [108]. Participants of the study conducted by Al-Majed and Preston (2000) shaved their heads at regular intervals (1-2 times per month) [110]. Therefore, that approximate time period was represented in the collected samples [110]. Detailed information on hair sample collection was not presented in the study by Black *et al.* (2011) [104].

Unadjusted and adjusted beta coefficients and 95%CIs for the effects of age, sex and fish consumption frequency estimated using data from all 5 studies and from studies with data from both males and females are shown in table 13. Inclusion of a variable representing geographic location did not improve the fit of this model. This may be due in part to the large proportion of individuals in the pooled dataset from the U.S (78.7%; 1,249/1,587). The inclusion of an interaction term for sex and fish consumption frequency improved the fit of both models. In the model using data from all 5 studies, females who ate 2-3 fish meals/week had on average 0.54 μg/g (95%CI: 0.16, 0.92) higher THg levels than males in the same category, adjusting for age. Conversely, females who ate ≥ 4 fish meals/week had on average 0.54 μg/g (95%CI: 0.024, 1.06) lower THg levels than males in the same category, adjusting for age (Figure 12). This is consistent with the results from the second model using data from 3 studies; however, the 95% CI for the beta-coefficient for the interaction produced by this model spanned negative and positive values, leaving uncertainty about the direction and magnitude of this effect modification (table 13). Age-adjusted β-coefficients and 95%CIs stratified by sex from models using data from all 5 studies and using data from studies 1-3 are shown in table 14.

Table 11: *Pooled Analysis 1: Distribution of population characteristics*

Characteristic	All Studies n = 1,593	Studies 1-3 ⌘ n = 356	Study 1 Black *et al.* (2011) [104] n = 97	Study 2 Elhamri *et al.* (2007) [105] n = 108	Study 3 Dong *et al.* (2015) [a] [106] n = 151	Study 4 Al-Majed & Preston (2000) [110] n = 133	Study 5 Xue *et al.* (2007) [108] n = 1,104
Age in years ± SD (Range)	30.5 ± 12.1 (4-86)	40.5 ± 19.7 (4-86)	28.7 ± 15 (4-70)	33.6 ± 14 (10-61)	53.2 ± 18.7 (16-86)	33.7 ± 8.03 (16-58)	26.9 ± 5.7 (15-43)
Sex							
Male	20% (332)	53% (189)	40% (39)	63% (68)	54% (82)	100% (133)	0
Female	80% (1,271)	47% (167)	60% (58)	37% (40)	46% (69)	0	100% (1,104)
Fish Consumption Frequency	73% (1,170)	50% (177)	12% (12)	40% (43)	81% (122)	18% (24)	88% (969)
≤ 1 meal/week	15% (238)	35% (125)	58% (56)	42% (45)	16% (24)	10% (13)	9% (100)
2-3 meals/week	12% (185)	15% (54)	30% (29)	19% (20)	3% (5)	72% (96)	3% (35)
≥ 4 meals/week							

⌘Characteristics of participants from studies 1-3 shown separately as both males and females are represented in these study populations

Table 12: *Pooled Analysis 1: Mean total mercury concentration in hair by population characteristics*

Characteristic	All Studies n = 1,593	Studies 1-3 ⌘ n = 356	Study 1 Black *et al.* (2011) [104] n = 97	Study 2 Elhamri *et al.* (2007) [105] n = 108	Study 3 Dong *et al.* (2015) [a] [106] n = 151	Study 4 Al-Majed & Preston (2000) [110] n = 133	Study 5 Xue *et al.* (2007) [108] n = 1,104
Overall Mean THg (µg/g) ± SD	0.77 ± 1.6	1.20 ± 2.30	0.23 ± 0.34	3.35 ± 3.24	0.30 ± 0.42	3.57 ± 2.43	0.29 ± 0.24
Sex							
Male	2.40 ± 2.76	1.57 ± 2.69	0.27 ± 0.25	3.76 ± 3.52	0.37 ± 0.52	3.57 ± 2.43	-
Female	0.35 ± 0.66	0.79 ± 1.67	0.21 ± 0.40	2.65 ± 2.61	0.20 ± 0.25	-	0.29 ± 0.24
Fish Consumption Frequency							
≤ 1 meal/week	0.32 ± 0.36	0.40 ± 0.45	0.24 ± 0.22	0.90 ± 0.40	0.24 ± 0.34	1.84 ± 0.84	0.27 ± 0.21
2-3 meals/week	1.13 ± 1.78	1.34 ± 1.90	0.21 ± 0.41	3.23 ± 2.02	0.41 ± 0.42	4.77 ± 2.27	0.40 ± 0.40
≥ 4 meals/week	3.08 ± 3.23	3.53 ± 4.31	0.27 ± 0.22	8.87 ± 1.90	1.07 ± 1.17	3.83 ± 2.52	0.33 ± 0.31

⌘
Characteristics of participants from studies 1-3 shown separately as both males and females are represented in these study populations

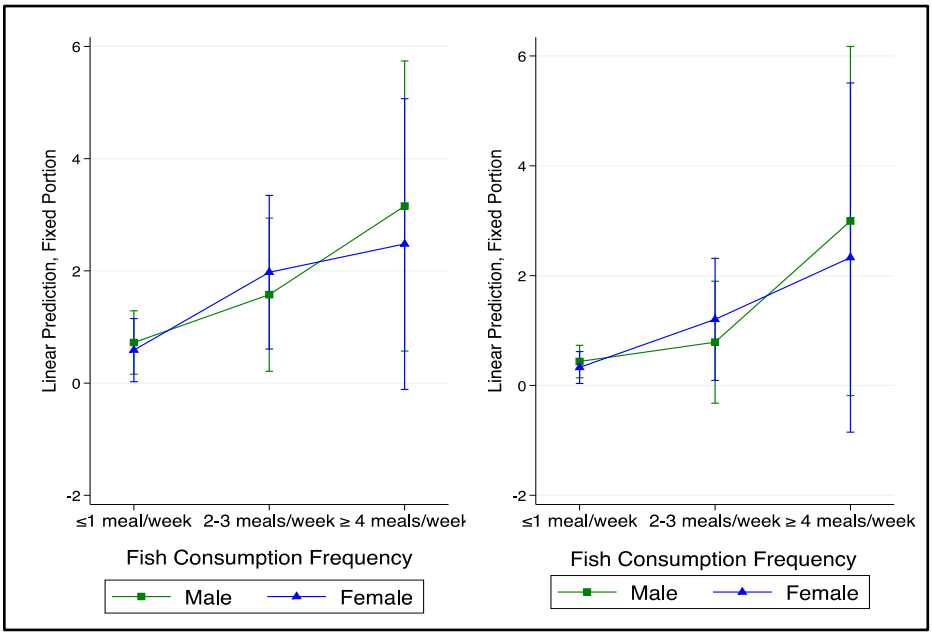
Table 13: *Pooled Analysis 1: Multi-level regression model estimates of the effects of fish consumption frequency on hair-mercury concentration (µg/g) adjusted for age and sex*

Characteristic	All Studies n = 1,593		Studies 1-3 n = 356	
	Unadjusted β (95% CI)	**Adjusted β (95% CI)**	**Unadjusted β (95% CI)**	**Adjusted β (95% CI)**
Age	0.0093 (0.003, 0.015)	0.009 (0.004, 0.01)	0.0064 (-0.0051, 0.018)	0.008 (0.005, 0.01)
Sex				
Male	*Reference*	*Reference*	*Reference*	*Reference*
Female	-0.43 (-0.66, -0.19)	-0.14 (-0.37, 0.10)	-0.42 (-0.80, -0.40)	-0.11 (-0.29, 0.07)
Fish Consumption Frequency				
≤ 1 meal/week	*Reference*	*Reference*	*Reference*	*Reference*
2-3 meals/week	1.10 (-0.02, 2.23)	0.85 (-0.42, 2.12)	0.65 (-0.32, 1.63)	0.35 (-0.73, 1.44)
≥ 4 meals/week	2.19 (-0.44, 4.81)	2.43 (-0.10, 4.97)	2.23 (-1.06, 5.51)	2.56 (-0.61, 5.73)
Interaction between Sex & Fish Consumption Frequency				
Male x ≤ 1 meal/week		*Reference*		*Reference*
Female x 2-3 meals/week		0.54 (0.16, 0.92)		0.52 (0.28, 0.77)
Female x ≥ 4 meals/week		-0.54 (-1.06, -0.02)		-0.56 (-0.88, -0.23)

Table 14: *Pooled Analysis 1: Adjusted estimates of the effect of fish consumption frequency on hair-mercury concentration (µg/g) stratified by sex*

	All Studies (n=1,593)				Studies 1-3 (n=356)			
	Among Males (n=322)		**Among Females** (n=1265)		**Among Males** (n=189)		**Among Females** (n=166)	
	n	β (95% CI)	n	β (95% CI)	n	β (95% CI)	n	β (95% CI)
Fish Consumption Frequency								
≤ 1 meal/week	112	*Reference*	1057	*Reference*	88	*Reference*	89	*Reference*
2-3 meals/week	80	0.85 (-0.42, 2.12)	158	1.39 (0.12, 2.66)	67	0.35 (-0.73, 1.44)	58	0.88 (-0.19, 1.95)
≥ 4 meals/week	130	2.43 (-0.10, 4.97)	50	1.89 (-0.65, 4.43)	34	2.56 (-0.61, 5.73))	20	2.00 (-1.16, 5.16)
Adjusted for Age and Study as a random effect								

Figure 12: *Pooled Analysis 1: Interaction between fish consumption frequency and sex (Left: All 5 studies; Right: studies 1-3)*



Heterogeneity Across Studies

The SDs representing the random intercept accounting for the effect of clustering in studies on baseline THg were 0.61 (95%CI: 0.31, 1.19) and 0.29 (95%CI: 0.14, 0.60) from the models using data from all studies and from only studies 1 to 3, respectively. In the analysis using data from all 5 studies, there was a high degree of residual variation across studies for the effect of consuming 2-3 vs. ≤ 1 meals/week on THg (µg/g) (SD: 1.42; 95%CI: 0.75, 2.69). The magnitude of the residual variation across studies increased for the effect of consuming ≥ 4 vs. ≤ 1 meals/week on THg (µg/g) (SD: 2.87; 95%CI: 1.54, 5.36). Similarly, among studies 1-3, estimates of the residual variation across studies for the effects of consuming 2-3 vs. ≤ 1 meals/week and ≥ 4 vs. ≤ 1 meals/week on THg (µg/g) were 1.09 (95%CI: 0.54, 2.19) and 3.21 (95%CI: 1.61, 6.44), respectively. Study quality indicators did not partially or completely explain this residual variation (data not shown).

In the analysis using data from all 5 studies, the SDs for the residual effects of being a member of each study on the estimated effects of fish consumption on THg (µg/g) indicated

the average spread around β-coefficients for each effect ranging from 1.42-2.87 μg/g. From the same analysis, for every one-year increase in age, total μg/g of mercury in hair only increased by 0.009 (95%CI: 0.004, 0.013), adjusting for sex and fish consumption. Given that one-year increases in age may not have meaningful impacts on the toxicokinetics of mercury, this analysis was repeated with age modeled as a categorical variable, so as to capture departures from linearity in the dose-response. The category boundaries and corresponding adjusted effect estimates were as follows: 0-20 years (reference); 21-30 years: β, 0.15 (95%CI: 0.027, 0.28); 31-40 years: β, 0.27 (95%CI: 0.14, 0.41); 41-50 years: β, 0.68 (95%CI: 0.47, 0.90); 51-60 years: β, 0.18 (95%CI: -0.09, 0.46); and >60 years: β, 0.31 (95%CI: 0.032, 0.58). The estimated effects of other variables in the model did not change substantially in response to modeling age as a categorical variable (data not shown). This comparison demonstrates that the combined effects of unmeasured characteristics explain more of the variation across study populations than age.

To assess whether the apparent increase in residual variation across studies for the effect of consuming ≥ 4 vs. ≤ 1 meals/week on THg (μg/g) was an artifact of modeling decisions, EVW conducted a sensitivity analysis. While using a more detailed exposure definition would theoretically improve effect estimation, this approach would have created categories with sparse data for some of the studies included in the analysis. For this reason, broader categories were used in the model, to increase the ability to estimate effects with an acceptable level of precision. However, broader exposure categories are susceptible to effect variation within categories, an issue that is particularly relevant when categories are open ended, such as the highest category of fish consumption frequency in Pooled Analysis 1 and 2 [86]. Consequently, one explanation for the increased variation in slopes across communities could be that on average, participants classified as eating ≥ 4 fish meals/week in some studies ate more fish relative to participants in this category in other studies. Using data from studies that measured fish consumption as number of meals/week, the highest number of meals/week among those who would be classified as eating ≥ 4 meals/week was: 10 among 29 participants from the study by Black *et al.* (2011) [104]; 5 among 20 participants from the study by Elhamri *et al.* (2007) [105]; 21 among 98 participants from the study by Al-Majed and Preston (2000) [110]; and 23 among 29 participants from the study by Xue *et al.* (2007) [108]. The mean number of meals/week among these subsets ranged from 4.4 (SD: 0.5) to 8.6 (SD: 4.8).

EVW repeated the analysis using datasets in which the fish consumption frequency variable was compatible with the following category boundaries: <1 meal/week (n=812); 1 meal/week (n=236); 2-3 meals/week (n=214); 4-6 meals/week (n=59); 7 meals/week (n=93) [104,105,108,110]. A total of 27 individuals from 3 studies were excluded because they reported consuming more than 7 fish meals/week. Results from this analysis showed a high degree of residual between-study variation for the effect of consuming 4-6 vs. <1 fish meals/week on THg concentration. The pooled β-coefficient for this effect was 3.05 (95%: -0.27, 6.36), adjusted for age and sex. The SD representing the magnitude of the residual variation across studies for this effect was 3.36 (95%CI: 1.67, 6.76). This means that on average, the effect of consuming 4-6 vs. <1 fish meals/week on THg concentration varies by an additional 3.36 µg/g across studies. The magnitude of the residual between-study variation decreased for the effect of consuming 7 vs. <1 fish meals/week on THg concentration. The pooled β-coefficient for this effect was 0.87 (95%: -0.58, 2.33), adjusted for age and sex. The SD around this effect was 1.23 (95%CI: 0.51, 2.98). While the magnitude of the SD decreased by more than half for the higher exposure contrast, it is still a substantial residual effect. This sensitivity analysis demonstrates that the high degree of the residual between-study variation for the effect of consuming ≥ 4 vs. ≤ 1 meals/week on THg (µg/g) estimated in the analysis was not an artifact of modeling decisions.

Pooled Analysis 2

The distributions of THg concentrations across population characteristics among datasets within which exposure status was defined with greater detail at lower consumption frequencies are shown in tables 15 and 16 [106–108]. The unadjusted and adjusted beta-coefficients and 95%CIs are shown in table 17. On average, males had slightly higher hair mercury concentrations compared to females, after adjusting for fish consumption frequency and age. There was no statistical evidence of an interaction between sex and fish consumption frequency in this analysis. Findings from this analysis showed that increasing fish intake was associated with increasing THg in hair (µg/g) (table 17). Given the low overall concentrations of mercury measured in hair samples from these populations, the magnitudes of the adjusted effect estimates for increasing fish consumption frequency were small.

Table 15: *Pooled Analysis 2: Distribution of population characteristics*

Characteristic	All Studies n=1,846	Study 1 Xue *et al.* (2007) [108] n=1,098	Study 2 Dong *et al.* (2015) [a] [106] n=151	Study 3 Karouna-Renier *et al.* (2008) [107] n=597
Age ± SD (Range)	31.3 ± 11.3 (15-86)	26.9 ±5.7 (15-43)	53 ± 18.9 (16-86)	34 ± 9.1 (17-49)
0-20 years	10% (185)	13% (141)	3% (4)	7% (40)
21-30 years	45% (835)	57% (628)	14% (21)	31% (186)
31-40 years	28% (521)	29% (313)	13% (20)	31% (188)
41-50 years	12% (218)	1% (16)	13% (19)	31% (183)
>50 years	5% (87)	0	58% (87)	0
Sex				
Male	5% (83)	0	55% (83)	0
Female	95% (1,763)	100% (1,098)	45% (68)	100% (597)
Fish Consumption Frequency				
None	12% (215)	11% (124)	5% (8)	14% (82)
1 meal/month	31% (574)	42% (462)	11% (16)	16% (96)
2-3 meals/month	26% (472)	19% (209)	35% (53)	35% (210)
≥ 1 meal/week	32% (586)	28% (303)	49% (74)	35% (209)

Table 16: *Pooled Analysis 2: Distribution of total mercury in hair by population characteristics*

Characteristic	All Studies n=1,846	Study 1 Xue *et al.* (2007) [108] n=1,098	Study 2 Dong *et al.* (2015) [a] [106] n=151	Study 3 Karouna-Renier *et al.* (2008) [107] n=597
Overall Mean THg (µg/g) ± SD (Range)	0.37 ± 0.71 (0.0044-22.1)	0.29 ± 0.24 (0.013 - 2.5)	0.30 ± 0.42 (0.0044 – 3.1)	0.55 ± 1.2 (0.022 – 22.1)
Age				
0-20 years	0.28 ± 0.79	0.20 ± 0.12	0.43 ± 0.34	0.55 ± 1.66
21-30 years	0.31 ± 0.36	0.28 ± 0.24	0.19 ± 0.32	0.45 ± 0.59
31-40 years	0.46 ± 1.10	0.35 ± 0.26	0.19 ± 0.37	0.66 ± 1.76
41-50 years	0.52 ± 0.60	0.27 ± 0.14	0.41 ± 0.68	0.55 ± 0.61
>50 years	0.31 ± 0.39	-	0.31 ± 0.39	-
Sex				
Male	0.37 ± 0.52	-	0.37 ± 0.52	-
Female	0.37 ± 0.72	0.29 ± 0.24	0.20 ± 0.25	0.55 ± 1.2
Fish Consumption Frequency				
None	0.16 ± 0.15	0.16 ± 0.11	0.15 ± 0.18	0.15 ± 0.20
1 meal/month	0.28 ± 0.49	0.26 ± 0.18	0.12 ± 0.10	0.43 ± 1.11
2-3 meals/month	0.36 ± 0.45	0.31 ± 0.23	0.25 ± 0.34	0.44 ± 0.61
≥ 1 meal/week	0.55 ± 1.07	0.37 ± 0.31	0.39 ± 0.51	0.89 ± 1.68

Table 17: *Pooled Analysis 2: Multi-level regression model results* [106–108]

Characteristic	β (95% CI)	
	Unadjusted	**Adjusted**
Age	0.0046 (0.0010, 0.0082)	0.002 (-0.002, 0.005)
Sex		
Female	*Reference*	*Reference*
Male	0.13 (-0.086, 0.34)	- 0.06 (-0.26, 0.15)
Fish Consumption Frequency		
None	*Reference*	*Reference*
1 meal/month	0.15 (0.037, 0.25)	0.14 (0.04, 0.25)
2-3 meals/month	0.20 (0.09, 0.31)	0.19 (0.08, 0.31)
≥ 1 meal/week	0.40 (0.16, 0.65)	0.39 (0.15, 0.64)

Heterogeneity Across Studies

The SD estimating the effect of clustering in studies not accounted for by the independent variables in the model on baseline THg (µg/g) was 0.074 (95%CI: 0.013, 0.44), showing a very small residual study effect. There was no residual between-study variation for the effect of consuming 2-3 vs. ≤ 1 fish meals/month. The SD representing residual between-study variation for the effect of consuming ≥ 1 fish meals/week was 0.20 (95%CI: 0.08, 0.49). The magnitude of the between-study effect is proportional to the effect sizes of covariates in the model and likely reflects the overall low mean THg among participants of these studies. This finding indicates that the combined effects of unmeasured characteristics explain variation in the magnitude of the effect of consuming 2-3 vs. ≤ 1 fish meals/month between studies to a greater degree than sex and age.

Discussion

Summary of Findings From the Meta-Analyses

The goals of the statistical analyses conducted for this review were to: characterize patterns of mercury exposure through fish consumption among populations represented in the available literature; Assess the degree to which the shape of the relationship between fish consumption frequency and tissue concentrations of mercury remains consistent across populations; and identify sources of heterogeneity across studies. We accomplished these goals by conducting two types of analysis: a meta-analysis of summary data presented in a subset of the selected literature; and multilevel regression analysis of raw data provided by

some authors. The two approaches to the meta-analysis conferred distinct advantages. Analysis of summary data presented in articles permitted the inclusion of a larger number of studies, and subsequently a more diverse set of populations was represented in the analysis. Analysis of pooled data is considered the ideal approach to meta-analysis [86]. Since the raw datasets were provided, statistical methods used in single studies could be applied to the merged data contributed by some authors [86]. These analyses had sufficient statistical power to precisely estimate the effects of fish consumption frequency on hair mercury concentrations, adjusting for multiple variables simultaneously, as well as assessing the presence of effect-measure modification [86].

Analysis of summary data presented in 13 articles yielded evidence of a dose-response relationship characterized by increasing mean THg with increasing fish consumption frequency in 11 of the studies. However, the shape of this relationship appeared linear in only a subset of the studies. Multivariate random-effects meta-regression models highlighted a large degree of variation in intercepts across studies for the effects of consuming 1-2 vs. <1 meal/week and ≥3 vs. 1-2 meals/week. This heterogeneity was only slightly reduced with the addition of a variable representing geographic location to the model. Visual assessment of the graphs in figure 10 revealed that this reduction was predominantly among studies conducted in North America, and more specifically the U.S. Similarly, results of pooled analysis 1 and 2 showed increasing μg/g of mercury with increasing fish consumption. However, the magnitude of the increases in THg associated with fish consumption frequency varied across sexes and subsets of studies. The magnitudes of the SDs in each of the models from the pooled analyses indicate a high level of variation across studies that is not explained by the covariates (fish consumption, age and sex).

Inferences drawn from each type of analysis were consistent with one another. Specifically, both types of analysis yielded evidence of a high degree of heterogeneity in the effect of increasing fish consumption frequency on hair THg concentrations (μg/g), with estimated magnitudes that were largest at the highest fish intake levels. A sensitivity analysis using pooled raw data from 4 studies demonstrated that the increase in the magnitude of residual between-study heterogeneity was not the result of the open-ended nature of the highest fish consumption frequency category. In both types of analysis, participant characteristics like age and sex did not account for much of the between-study heterogeneity.

Heterogeneity from Species of Fish, Shellfish & Marine Mammals Consumed

Few study reports had detailed information about the species of fish or seafood that participants consumed or where they came from. This information should be considered, given that the degree of mercury contamination has been shown to vary across species with different sizes and habitats [63]. In the pooled analyses, random slopes for effect of each fish consumption level on hair THg (µg/g) showed a high degree of variation across studies that was not explained by age and sex. The observed effect of consumption level could reflect differences in the species consumed by people in each category, rather than variation in the magnitude of the effect of eating more. However, if all members of the same study population tend to eat the same types of fish or seafood, independent of the frequency, differences in the species consumed across study populations does not explain the magnitude of the SDs for the random slopes estimated in these analyses. In this context, average hair THg (µg/g) among study populations that usually consume fish or seafood with a greater capacity to accumulate Hg would be higher than among populations that consume fish or seafood with lower levels of contamination. However, if the relationship between intake and tissue concentrations remained the same across study populations, the study-specific slopes should be similar. This effect would be captured by the random intercept, which represents variation in hair THg (µg/g) when all covariates are at their reference values. In Pooled Analysis 1 and 2, random intercepts showed some variation in baseline values of THg (µg/g) in hair that is not explained by age and sex.

Sex-Related Differences in Mercury Toxicokinetics

Pooled analysis 1 yielded evidence of an interaction between sex and fish consumption frequency, suggesting the presence of sex-related differences in mercury toxicokinetics. The potential for variation in the toxicokinetic properties of mercury across biological sexes has been acknowledged in the scientific literature [63]. However, it has been noted that more research is needed to fully characterize the nature of this variation under different exposure scenarios [63]. Animal models have yielded evidence that on average the whole body retention of mercury is higher in males when compared to females [63,198,199]. Nielsen *et al.* (1994) investigated sex-related variation in mercury accumulation in the hair, blood and muscle of mice as indicators of total body retention [199]. Results from this experiment showed higher deposition of mercury in the hair of male mice, compared to female mice [199]. Thomas *et al.* (1982) reported persistence in sex-related variation in whole body elimination of mercury following adjustment for body weight, indicating that higher body mass and faster growth rate among male rats did not completely explain this variation [198].

Some evidence generated in studies of human populations is consistent with these findings. Among articles included in this review, 6 presented mercury concentrations stratified by fish consumption frequency and sex (Tables 2 and 4) [109,117,127,171,180,190]. In studies by Chen *et al.* (1990) [117], Dickman *et al.* (1999) [127], Johnsson *et al.* (2004) [109] and Faial *et al.* (2015) [190], hair mercury concentrations were higher among males than females in the same exposure categories. Similarly, in the study by Tsuji *et al.* (2012) mercury concentrations in blood were higher among males compared to females in the same categories of fish consumption frequency [180]. However Masih *et al.* (2016) reported no difference in mean concentrations of mercury in hair between males and females who ate fish at the same frequency [171]. Some authors have proposed hypotheses that could explain sex-related differences in mercury toxicokinetics [198,199]. Thomas *et al.* (1982) have posited that these differences could be related to hormonal differences between males and females [198]. However, further research is needed to explore this hypothesis and others that may contribute to a better understanding of sex-related differences in tissue concentrations of mercury.

Limitations

Findings from the systematic review and meta-analyses may be affected by publication bias, given that this review was limited to the published literature [86]. Publication bias can be defined as the systematic tendency to preferentially report certain types of results over others [86]. Specifically, findings from larger studies and those that produce estimates consistent with expected or desired results may be preferentially selected for publication [86]. Additionally, the decision to exclude studies that did not present estimated tissue concentrations of mercury stratified by fish consumption frequency could have resulted in selection bias in the meta-analysis [86].

Since characteristics were measured at the study level, a limitation of the multivariate random-effects meta-regression is the small number of studies eligible for inclusion (n=13). This constrained the capacity to generate valid estimates of the influence of multiple characteristics at a time on heterogeneity across studies, because doing so leaves only a few studies in each stratum. In models with multiple covariates, sparse data could impact the performance of the multivariate random-effects method, because this method employs the quadratic approach to approximating the maximum likelihood, which is susceptible to poor performance in the presence of sparse data [102].

The pooled analyses were limited by lack of available data on factors hypothesized to influence mercury toxicokinetics, required for quantification of the impact of each of these factors on heterogeneity across studies. For example, adjustment for pregnancy status was not possible, because this information was not available for some of the studies. If being pregnant or breastfeeding impacts the distribution of ingested mercury in the body, this mechanism could be responsible for part of the residual variation across studies that include women at this life-stage. Additionally, variation in the composition of the overall diet of participants could explain some of the variation in hair mercury concentrations. Some evidence suggests that dietary components such as fibre and phytate may influence the bioavailability of mercury from fish [63]. Further, variation in dietary intake of selenium may explain some variation in hair mercury concentrations across studies. Selenium is an antioxidant and essential nutrient that has been shown to interact with Hg by bonding competitively with Hg compounds [63,69,200–204]. Selenium intake is known to influence the toxicity of mercury and may play a role in altering bioavailability of Hg if the source of the ingested selenium is the Hg-contaminated fish [63,69,200–204]. Finally, insufficient data on the species of fish and seafood consumed precluded assessment of the extent to which differences in the distributions of fish and seafood subtypes contributed to variation across studies. However, while estimation of the influence of each of these characteristics was not possible, the random-effects models provided an estimate of the combined influence of unmeasured characteristics on THg in hair.

An additional limitation is that each study measured THg, but most lacked information on sources of THg exposure other than fish. For example, dental amalgams are a common source of exposure to elemental mercury, which has similar toxicokinetic properties to methylmercury [63,64,66,67,69,71]. From the pooled analysis, in the studies by Karouna-Renier *et al.* (2008) [107], Xue *et al.* (2007) [108], Black *et al.* (2011) [104] and Dong *et al.* (2015) [a] [106] data on whether participants had dental amalgams were not collected. Of note, none of the participants of the studies conducted by Elhamri *et al.* (2007) [105] and Al-Majed and Preston (2000) [110] had dental amalgams. Similarly, of studies included in the analysis of summary data, articles by Knobeloch *et al.* (2007)[132], Lincoln *et al.* (2011) [149], Olivero-Verbel *et al.* (2011) [150], Traynor *et al.* (2013)[155], Schaefer *et al.* (2014) [161], Bonsignore *et al.* (2015) [112], Dong *et al.* (2015) [b] [170] did not include any information on whether participants had dental amalgams. The prevalence of dental amalgams in the remaining studies was: 13% in the study by Salehi & Esmaili-Sari (2010) [141]; 38% in the study by Okati *et al.* (2012) [153]; and 26% in the study by Michalak *et al.* (2014) [160]. If the degree of exposure to mercury through

other sources is not proportional across categories of participants consuming different quantities of fish, this could explain some of the variation in the effect of fish consumption on hair THg across studies.

Contribution to the Scientific Literature & Risk Assessment Methodology

The systematic literature search conducted for this analysis shows this to be the first comprehensive systematic review summarizing the published literature presenting biomarker concentrations of mercury stratified by fish consumption frequencies in populations worldwide. Previous reviews have focused on specific population subgroups and have not been restricted to articles presenting stratified estimates of mercury concentrations [205,206]. Further, this is the first meta-analysis of data from human populations aimed at investigating the presence and shape of a dose-response relationship between fish intake and hair-mercury concentrations and quantifying heterogeneity across subgroups. Assessment of the extent to which commonly made assumptions about the presence and shape of this dose-response relationship hold true is crucial to ensuring the validity of exposure assessment methods used in research and regulatory settings. The use of advanced statistical methods to analyze these properties in the available body of research advances the science on human exposure to mercury through fish.

Findings of a positive association between internal dose of mercury and fish consumption frequency are consistent with conventional knowledge about this relationship. However, these analyses highlight that the concern that commonly made assumptions about the shape of that relationship may be violated in certain subsets of the population. In a research setting, fish consumption frequency is often measured as a continuous variable and modeled as such in statistical analyses. The validity of this approach rests on the assumption that the relationship between internal dose of mercury and fish consumption frequency is strictly linear. While this assumption may not be violated in certain settings, these analyses indicate that it should be assessed carefully. Assumptions about linearity are also implicit in methods used to estimate ingested dose, which is used as a proxy for internal dose in risk assessments conducted by regulatory bodies. In this context, multiplicative equations are used to estimate average daily intakes using fish muscle consumption and MeHg concentrations measured in fish [69,87]. The product of these terms is often divided by body weight, which is either known or estimated based on sex and age category [69,87]. Further, results of the meta-analyses emphasize a high degree of heterogeneity in internal dose of mercury across studies that is not explained by the distribution of characteristics like age

and sex. This finding suggests that more accurate assessment of health risks associated with ingestion of fish require consideration of more individual characteristics.

Recommendations for Future Research

In general, it is crucial for the chosen methods for measuring dietary intake of a given food or nutrient to correspond to the characteristics of the selected tissue for biomarker analysis. Specifically, the time window during which dietary habits are measured should correspond to the window represented in the chosen tissue. Additionally, the inherent limitations on inferences drawn from studies that use each tissue need to be considered when interpreting the findings. In the context of measuring the internal dose of Hg, and MeHg in particular, hair should be the chosen matrix. Dietary intake measurement methods should aim to capture the period of time represented in the collected hair strands. The exposure period represented in the collected hair samples can be standardized by making note of the root-end of the strand and cutting all samples to the same length. It should be noted, however, that designing dietary intake measurement tools to correspond to the standardized hair length requires making assumptions about consistency in hair growth rates across participants, which may be violated [92,207]. Alternately, entire strands can be analyzed and FFQs measuring long-term intake can be used. To account for varying exposure periods represented in hair strands of different lengths and potential decreases in reliability of measurements in longer hair, statistical models can include adjustment for hair length [92,207]. If THg is the biomarker selected for analysis, exposure to additional sources of mercury should be measured concurrently.

Findings from this meta-analysis demonstrate that accurate assessment of exposure to Hg through fish consumption requires consideration of more individual characteristics than age and sex. Future research should aim to investigate the relative importance of additional factors that may be associated with variation in the relationship between fish consumption frequency and measurements of the internal dose of mercury. Hypothesis-screening studies would be useful to collect general and broad information that can be used to identify new lines of inquiry for more in-depth investigation of the relationship between dietary intake of Hg and internal dose as measured through biomarkers [86]. Detailed data on the species of fish or seafood consumed should be collected. However, dietary data should not be limited to hypothesized sources of Hg exposure. Given the potential for other nutrients in the diet or overall diet composition to impact the toxicokinetic and toxicodynamic properties of Hg, data on these factors should be collected [63]. New research should aim to explore genetic factors that influence Hg toxicokinetics, which have the potential explain some variation across

populations [63]. Once a body of evidence containing detailed data on a broader range of participant characteristics has been generated, meta-analyses like the ones presented in this paper should be repeated.

Conclusions

Mercury presents a substantial public health concern, and therefore has been the focus of a large body of research investigating exposure and toxic effects in humans. The purpose of this systematic review was to summarize published research on the relationship between fish consumption frequency and biomarker concentrations of mercury. Following a comprehensive article selection process, 87 studies were included in the review. The included studies were conducted in various countries around the world, with the highest number of studies being conducted in the United States. This review showed that populations around the globe have measurable levels of mercury in their tissues, which is consistent with actions taken by international agencies to stress the importance of careful monitoring of populations for mercury exposure [81].

Hair mercury concentration was used as the outcome in meta-analyses that aimed to quantify how much this relationship varies across studies and the extent to which population characteristics explain that variation. These analyses showed that the relationship between fish intake and hair mercury level varies considerably across studies. In regression models using raw data provided by some authors of the included literature, variation across studies was not explained by characteristics like age and sex. These findings indicated that research on additional factors associated with variation across individuals and populations is needed, to better understand health risks associated with consuming fish. These analyses also yielded evidence of an interaction between sex and fish consumption frequency, characterized by higher hair mercury concentrations among males when compared to females who consume roughly the same amount of fish. Although the potential for sex-related differences in the toxicokinetics of mercury have been addressed in the scientific literature, more research is needed to better understand these effects.

Chapter 3: Patterns of Fish and Marine Mammal Consumption and Concentrations of Methylmercury in Hair Among Residents of Western Canadian Arctic Communities

Introduction

Mercury is a chemical element with three valence states, elemental mercury (Hg^0), divalent inorganic mercury compounds (Hg^{2+}), and organic compounds. Given their capacity to induce potent toxicological effects in humans, contamination of the environment with mercury compounds represents a substantial environmental health concern. For this reason, mercury has been the focus of a large body of research aiming to better understand the mechanisms through which it enters the environment, as well as pathways for human exposure and subsequent toxicological effects (Chapter 2 of this dissertation).

Mercury is stored in geological reservoirs within the earth's crust in its elemental form [63,65,208]. Release from these reservoirs occurs through geological weathering, defined as the alteration or breakdown of rocks and minerals by mechanical and chemical processes [33,63,65,209]. Weathering is a natural process through which changes in the earth's surface occur over time [63,209]. In this context, weathering results from: changes in temperature or pressure; exposure to wind and water; or volcanic events [63,209]. However, anthropogenic activities also contribute to weathering and subsequently accelerate the release of elemental mercury from geological reservoirs [63,65–69,208–210]. Industrial activities that directly impact mobilization of mercury include mining, which breaks down rock mechanically, and burning fossil fuels, which releases chemicals that can alter the composition of rocks [63,65–69,208–210]. Indirectly, human-caused global climate change affects the release of mercury by inducing changes to the carbon cycle that are conducive to chemical weathering [32,33,208]. Finally, some human activities lead to direct release of mercury into the environment, including: burning fossil fuels; industrial processes involved in the production of gold, cement and chloralkali; and medical and municipal waste incineration [63,65–69,208,210]. Following mobilization, mercury undergoes biogeochemical cycling on a global scale; a complex process characterized by several intersecting phases that result in the formation of inorganic and organic mercury compounds [33,63,65].

Once present in aquatic systems, a portion of mercury is chemically transformed into methylmercury (MeHg), a process mediated by anaerobic organisms that involves the formation of a covalent bond between an inorganic mercury ion and a methyl group [63,65–67,210]. This transformation is thought to occur most often in wetland ecosystems and the surface of lake sediments [65]. As an organic compound, MeHg is lipophilic and mobile, with the capacity to enter the plasma membrane of cells and accumulate in the cytoplasm [63,65]. This property has important implications for bioconcentration of MeHg in aquatic organisms and subsequent biomagnification in aquatic food chains [63,65–67,210]. Specifically, the presence of the compound in the cytoplasm of the cells allows for transfer of MeHg between trophic levels of aquatic food chains, whereas inorganic forms are predominantly membrane bound and less likely to concentrate in organisms at higher trophic levels [63]. The concentration of MeHg in aquatic organisms has been shown to be greater than that of the ambient water by a factor $\geq 10^{(6)}$ [63,65].

MeHg contamination of aquatic ecosystems is considered the most abundant non-occupational source of human exposure to mercury [63,66–69,210]. The primary source of MeHg exposure in humans is consumption of fish or fish products and marine mammals, with larger, longer-living fish posing greater risk of toxic exposure [63,66–69,210]. Population subgroups that are particularly susceptible to this contaminant are sport or subsistence fishers residing in Arctic communities [63,66,71,210]. The disproportional threat posed by Arctic fish is due to: greater emissions of elemental mercury in the northern hemisphere; changes to the global climate altering the mercury cycle; and periodic or regular consumption of species with a greater potential for high levels of organic mercury contamination [63,66,71,210]. Additionally, sport and subsistence fishers do not benefit from regulatory measures that control the mercury content of commercially sold fish products.

Research on exposure to mercury among Indigenous residents of the Canadian Arctic has typically focused on coastal populations that consume large amounts of marine mammals [211]. This is reasonable, given the greater capacity of these large species to accumulate mercury. However, residents of inland communities in the western Canadian Arctic are part of the target audience for territorial public health messages about fish consumption, without concurrent assessments of human exposure levels [212,213]. Unpublished ethnographic research conducted by the author among residents of western Canadian Arctic communities revealed their concerns about the extent to which mercury has accumulated in their bodies and the relationship between their fish and marine mammal consumption habits and

mercury concentrations in their tissues. In response, this research aims to analyze data collected from residents of inland communities in the Canadian Arctic to: characterize fish and marine mammal consumption patterns; biochemically measure the mercury level in hair samples to ascertain individual exposure to mercury; and assess the relationship of the internal dose of mercury to fish and marine mammal consumption, other dietary components and participant characteristics.

Methods

Study Design

This mercury exposure project was conducted to investigate the association between mercury exposure and gastric health outcomes as an environmental health component of ongoing community-driven projects led by the Canadian North *Helicobacter pylori* (CAN*Help*) Working Group in western Canadian Arctic communities (www.canhelpworkinggroup.ca). The CAN*Help* Working Group was established in 2007 in response to concerns raised by community representatives about *H. pylori* infection and gastric cancer risk. This research program is a collaborative effort, linking northern Canadian Indigenous communities, their health care providers and regional health authorities with investigators from a variety of disciplines at the University of Alberta [214,215]. To conduct a comprehensive investigation of the burden of *H.pylori* infection and associated disease in northern Indigenous populations, projects that incorporated an array of scientific disciplines and research designs were established in each community at the request of community leaders [214]. A local planning committee guided the conduct of each project and ensured that research activities were culturally appropriate and in keeping with community priorities [214]. This research received ethics approval from the University of Alberta Health Research Ethics Board, as a component of the project "Addressing Community Concerns about Risks from *H.pylori* Infection in the Circumpolar North"; Study ID: MS21_Pro00007868, Amendment ID: Pro00007868_AME17, with an approval date of September 19, 2016.

Person, Place and Time

The mercury exposure project was conducted within three CAN*Help* Working Group community projects. The first of these projects launched in 2007 in the hamlet of Aklavik, Northwest Territories (NT) (2006 census population=590, ~92% identifying as Gwich'in [Athabascan First Nation] or Inuvialuit [Inuit]) [16,17]. Projects began in 2010 in Old Crow, Yukon (YT) (2011 census population=245, ~85% identifying as Vuntut Gwich'in [19,22], and in

2012 in Fort McPherson, NT (2011 census population=844, ~90% Tetlit Gwich'in) [25]. The communities participating in CAN*Help* Working Group projects are located in remote regions of the western Canadian Arctic. Aklavik and Tuktoyaktuk are accessible by water or air in the summer and ice road in the winter [19–21]. Fort McPherson is accessible by road with a ferry crossing in the summer and ice road in the winter [19–21]. Old Crow is accessible only by air [19–21]. Many residents of these communities continue to follow a traditional lifestyle of hunting, trapping and fishing, while adopting modern technologies such as computers and snowmobiles [19–21]. Participation in the mercury exposure project was open to all residents of these three communities during September-November 2016. Recruitment activities involved radio announcements, social media posts, flyers on community message boards, and directly contacting participants of CAN*Help* Working Group projects for which current contact information was available.

Choice of Tissue for Biomarker Analysis

Evidence suggests that hair is the biological medium best suited for measuring MeHg exposure [63,69,85,93,105,131,216–224]. Hair from the scalp is a commonly selected matrix for biomonitoring of MeHg exposure, because MeHg accounts for approximately 80% of the total mercury found in hair and can be measured directly [63,69,85,93,105,131,216–224]. There are also several practical advantages to collecting hair samples, relative to other traditionally used matrices like urine and blood, including: chemical stability; simple and non-invasive sampling; ease in storing, transporting and archiving specimens; and relatively low cost [82,85,92,98,99].

Exposure Time Window

It is estimated that among healthy individuals the growth rate of scalp hair can range from 0.6 to 3.36 cm/month, with an average rate of 1 cm/month [82,92,98]. Therefore, depending on the length of an individual's hair, the concentration of mercury measured is considered reflexive of exposure over the past few months. Input from local planning committees highlighted that on average, residents of participating communities consume the greatest amount of fish and marine mammals during the spring and summer seasons. For this reason, hair sample collection took place during the fall season (September-November).

Hair Sample Collection

The procedures for collecting hair samples were adapted from protocols outlined by the United States Centers for Disease Control (CDC) for use in the National Health and Nutrition Examination Survey (NHANES) [225]. The lead author (PhD candidate EVW) collected all hair

samples from the occipital region of the scalp using stainless steel shears, obtaining a minimum of 120 mg of hair from each participant to allow for duplication of the laboratory measurements for quality assurance/quality control (QA/QC) purposes. To ensure enough hair was obtained from each participant, EVW used a high precision digital scale to weigh the sample immediately following collection. Given that hair length corresponds to the exposure period represented in the strand, EVW also measured hair length (in cm) at this time, using a ruler to ensure accurate documentation, before transferring samples into a zip closable plastic bag and applying a label specifying the sample ID number, collection date, sample weight and hair length. Additionally, EVW recorded information on use of permanent hair treatments, including hair dye or permanent waves, and time since the most recent treatment.

Laboratory Analysis of Samples

The collected hair samples were analyzed by the University of Alberta Biogeochemical Analytical Service Laboratory (BASL). This lab has been accredited by the Canadian Association for Laboratory Accreditation (CALA) as meeting ISO/IEC 17025 standards for the performance of specific tests. MeHg was measured in the full-length of each hair sample using gas chromatography inductively coupled plasma-mass spectrometry (GC-ICP-MS) [226,227]. Quality control methods employed by the lab included the use of reference material 1AEA-085 for MeHg, total mercury and other trace elements in hair. Single point calibration was applied, and the calibration standard was analyzed in 4 replicates. The relative standard deviation for the ratio of Hg isotope 201:202 was considered acceptable if the value was less than 5%. If the value was greater than 5%, the calibration was repeated. Instrument and method blanks and a second source reference material were also used to monitor contamination with MeHg, accuracy and instrumental drift during analysis. These were incorporated into the analysis at a frequency of 1 per batch of approximately 30 samples. The instrument was re-calibrated if the second source reference material measurements were outside of the 80-120% recovery range. Additionally, water samples were spiked with a known quantity of enriched MeHg isotope ($CH_3{}^{201}Hg$) as an internal standard. Finally, laboratory duplicates were performed at a frequency of 1 per 5 samples. For added quality assurance, EVW divided approximately 10% of the samples and submitted them to the lab as separate individuals. Additionally, lab personnel were blinded to all participant characteristics, including age, sex and the amount and types of fish and marine mammals consumed.

Fish and Marine Mammal Consumption Data

In consultation with representatives from participating communities, EVW designed a Food Frequency Questionnaire (FFQ) focused on fish and marine mammal consumption. Community input guided the selection of fish species for inclusion in the FFQ. Additionally, community representatives guided incorporation of familiar names and descriptions for locally harvested fish, to ensure respondents had a clear understanding of the item being asked about. All participants completed the interview in English. Planning committee members highlighted Beluga Whale (*D.leucas*) as the only marine mammal regularly consumed by residents of participating communities. The FFQ measured consumption frequencies as average number of times each type of fish or whale was consumed per week (in the subsequent text, food consumption events will be referred to as "meals"). Validation studies have shown that attempting to ascertain portion size does not appreciably improve overall characterization of diet, due to the general inability of individuals to recall portion sizes accurately [28]. To reduce the burden on participants, the food frequency questionnaire did not include portion size. To capture seasonal variability in consumption, the FFQ asked respondents to specify the time of year in which they typically harvest each type of fish or marine mammal that they reported consuming. The FFQ then asked respondents the typical number of meals per week of each species during the time of year they are harvested. Since it is common for community members to preserve harvested fish by drying, freezing or smoking the meat, the FFQ asked respondents to report the frequency of consuming each species during other parts of the year. Given the potential for preparation methods to alter the bioavailability of mercury in fish meat, the FFQ also asked participants to specify how they typically prepare each type of fish/whale for eating and the parts of fish they consume [228]. Most participants were able to identify the specific species they consumed; pictures were available for those who were unsure. The potential for the overall composition of an individual's diet and intake of specific nutrients to directly or indirectly influence the toxicokinetic properties of MeHg has been described in the scientific literature [229]. For this reason, the FFQ collected data on other dietary components, including average weekly intake of: fruit, fresh fruit juice, raw and cooked vegetables, fresh or packaged milk and yogurt.

Exposure Definition

Fish and marine mammal consumption, ascertained by the FFQ designed for this study, constituted the source of mercury exposure examined for this analysis. Options on the FFQ were formatted as open-ended, yielding continuous variables that represent the average

meals per week of each food item. The structure of the FFQ permitted the creation of separate variables representing the usual frequency of consuming each reported species in each of the four seasons. Additionally, EVW generated season-specific variables to represent total fish or marine mammal meals per week by summing the weekly number of meals in each season across species. Input from local planning committees indicated that there was too much variation across seasons with respect to the frequency and types of fish/whale consumed to allow combining consumption events by estimating an overall average.

Outcome Definition

The outcome for this analysis was the MeHg concentration measured in hair samples in units of µg/g on a continuous scale. Guidelines generated by Health Canada for interpreting the degree of risk associated with hair-mercury levels provide perspective for interpreting values [230]. According to these guidelines, hair mercury concentrations of ≤ 6 µg/g are considered acceptable for adult males and females who are not pregnant or breastfeeding [230]. Among children under the age of 12 and women who are pregnant, breastfeeding or of reproductive age, concentrations ≤ 2 µg/g are considered acceptable [230].

Statistical Analysis

The goal of the statistical analysis was to estimate the association between fish and marine mammal meals per week and hair MeHg concentration among participants from the three western Canadian Arctic communities selected for this project. All statistical analyses were conducted using STATA© SE v.12. EVW constructed a multivariable linear regression model to estimate beta coefficients and 95% confidence intervals (CIs) as measures of the association between characteristics of interest and MeHg concentration (µg/g) measured in hair. Because participants residing in the same community cannot be assumed to be independent with respect to study variables, the model included clustering in communities as a random effect, giving each community its own intercept. The benefit of this approach is that it allows each community to have its own baseline value of hair-mercury concentration in the intercept, to which the effects of all covariates are added. The standard deviation (SD) of the random community effect measures the extent to which baseline values across communities deviate from the population mean of all communities combined, and represents the magnitude of the effect of clustering in communities. The magnitude of the community effect depends on the extent to which covariates in the model explain differences in mean MeHg concentration across communities. Most participants in this analysis (75%) did not have other household members among participants, so clustering in households was not a concern.

To avoid making the assumption that the relationship between increasing consumption of respective food items and hair mercury levels was linear, each variable was converted to a categorical format. When possible, category boundaries were defined so that there was no more than a two-fold increase in number of servings within a category [28]. The purpose of this was to generate categories within which the effect of interest does not vary substantially and therefore more valid exposure contrasts [28,86]. However, if data were too sparse to permit the use of optimal category boundaries, adjacent categories were collapsed to improve statistical precision. To confirm whether these variables could be modeled as continuous, the linearity of the relationship between hair MeHg concentration and the continuous forms of each variable was also visually assessed using a lowess plot (bandwidth: 0.80). The presence of a trend between MeHg concentrations (µg/g) in hair and fish/whale consumption frequency was detected using an extension of the Wilcoxon rank-sum test for testing trends over ordered groups that incorporates a correction for ties [231].

EVW used purposeful selection, as proposed by Hosmer and Lemeshow (2000), to identify the best set of adjustment variables for each of the season-specific exposure variables [232]. This method follows a change-in-estimate approach, with variable selection decisions, including interaction terms, based on the extent to which each potential covariate influences the magnitude of exposure effects of interest [86,232]: All potential covariates were included in a multivariable random effects model and subsequently removed one at a time. If the coefficient of any independent variable changed by ≥10% with the removal of a given covariate, the removed variable was included in the final model [86,232], unless there was evidence of collinearity with other selected variables; when collinearity was apparent, likelihood ratio tests were used to select the best set of adjustment variables. Variables considered for inclusion in the model were: age, sex, use of permanent hair treatments, the proportion of consumed fish or marine mammal species harvested from the ocean or local rivers, the proportion of consumed species usually prepared by cooking (versus eaten raw, dried or smoked), and other dietary components, including fruits and vegetables, dairy products or regular use of dietary supplements. Hair length was automatically included in the final model to account for variation in the exposure period represented in hair strands of different lengths. The presence of interactions between fish/whale consumption frequency in each season and all other independent variables in the model was tested using the Likelihood-ratio test.

EVW used model checking procedures proposed by Rothman, Greenland and Lash (2008) [86]. Sensitivity analysis assessed the extent to which modeling decisions impacted inferences drawn from the analysis [86]. The chosen formats for modeling each variable were checked by generating models using alternative variable formats and comparing the generated estimates and overall model fit using the likelihood-ratio test. Continuous or interval variables were modeled alternately on a continuous scale, with linear or cubic splines, and in categorical formats. The extent to which category boundaries influenced inferences about trends was assessed by creating variables with alternate between-category cut-points and comparing the model results.

Community Effect

Although data were insufficient for estimating species-specific effects, some of this effect was likely picked up by the random effect, given the considerable variation in fish/whale species consumed across communities. A sensitivity analysis explored the extent to which variation in species consumed by participants from different communities explained the residual variation. EVW inspected community-specific patterns of fish/whale consumption to identify species most likely to discriminate between communities based on the relative frequencies of their intake. The correlation between species-specific and total fish/whale consumption frequencies were considered low enough to permit inclusion in the same model if the correlation coefficients were < 0.7 [86,232]. The variables representing intake of the selected species were then added to the model for each season, to quantify changes in the residual variation across communities as measured by the SD. Given that data were limited, the linearity of the relationship between consumption of each species-specific consumption variable was assessed visually using lowess plots to see whether they could be modeled as continuous.

Bias Analysis

Given the potential for MeHg measurement error to produce outcome misclassification, EVW conducted a quantitative bias analysis using the measured hair-mercury concentrations among duplicated samples as parameters. The percent change between analyses of the same participant's hair was calculated. To achieve this, the value obtained during the repeat analysis of an individual's sample was subtracted from the originally measured value and the difference was divided by the originally measured value. For participants with more than 2 measurements, the largest difference between measured concentrations was used. To quantify the extent to which measurement error influenced inferences drawn from this

analysis, the originally measured MeHg value was adjusted in two ways. First the overall mean percent change and the proportion of the repeated measurements that increased or decreased in value were used to estimate the magnitude of measurement error and frequency of change in either direction in the entire study population. Second, the mean percent change between repeated measurements and the proportion that increased or decreased were stratified by participant characteristics to apply stratum-specific estimates of the magnitude and direction of measurement error to corresponding subsets of participants, selecting at random the participants assigned increasing or decreasing MeHg concentrations. All analyses were repeated using the adjusted MeHg concentrations as outcome variables.

Results

Combining the three selected western Canadian Arctic communities, 101 individuals provided hair samples and diet data (42 from Aklavik, NT; 32 from Old Crow, YT; and 24 from Fort McPherson, NT). Participants were nearly all Indigenous, predominantly identifying as either Gwich'in (60%; 60/101) or Inuvialuit (30%; 30/101). A small proportion of participants were of European descent (6%; 6/101), but had been residing and active participants in the community for at least 5 years. The study population was disproportionately female (63%; 64/101); none of the female participants were pregnant or breastfeeding at the time of data collection. The mean age among all participants was 52 (SD: 15.7; Range: 10-86) years. Assuming an average growth rate of 1 cm/month, the exposure periods represented in the collected hair samples ranged from approximately 3 weeks to almost 9 years (median: 1.1 year; IQR: 2.1 years).

Patterns of Fish and Marine Mammal Consumption

Almost all participants (96%; 97/101) reported eating fish or marine mammals in the past 12 months. The data obtained from the fish-focussed FFQ was consistent with input from local planning committees, which highlighted the summer as the main season during which community members consume fish/whale. However, there was considerable variation by species and community (Figure 13). A total of 17 different species of fish or marine mammals were consumed by participants in the previous 12 months (table 18). The most commonly consumed species of fish was Broad Whitefish (*C.nasus*) (83%), followed by Inconnu (*S.nelma*) (42%) and Dolly Varden (*S.malma*) (33%). A large proportion of participants also ate Beluga Whale (*D.leucas*) (42%), although 71% of those who reported eating Beluga Whale in the past 12 months were from Aklavik, NT (30/42), the community

with the largest proportion of Inuit residents. Table 19 shows the five most frequent species consumed ≥ 1 time/week by community and season. The mean number of different species eaten by participants was 3.5 (SD: 1.9; Range: 0-9). The main waterways and sites from which participants harvest fish and marine mammal species are shown in figure 14. On average, participants harvest most of the species they consume from local rivers, followed by the ocean and nearby lakes. The mean proportions of species consumed by each participant that were harvested from each type of waterway were as follows: rivers 66.7% (SD: 32.9%; Range: 0-100%); the ocean 21.7% (SD: 27.4%; Range: 0-100%); and lakes 1.8% (SD: 8.2%; Range: 0-50%). Additionally, the mean proportion of consumed species purchased from the store was 2.0% (SD: 7.6%; Range: 0-33%).

Table 18: *Fish and marine mammal species consumed by participants at least one time in the previous 12 months among*

Species of Fish or Marine Mammal		Proportion that Consumed Each Species in the Past 12 Months					
		Aklavik (n=45)		Old Crow (n=32)		Ft McPherson (n=24)	
Scientific Name	**Common Name**	**n**	**%**	**n**	**%**	**n**	**%**
Salmonidae Family							
Salvelinus aplinus	Arctic Char	11	24	3	9	1	4
Salvelinus malma	Dolly Varden	30	67	0	0	3	13
Salvelinus namaycush	Lake Trout	1	2	0	0	5	21
Coregonus nasus	Broad Whitefish	36	80	26	81	22	92
Coregonus clupeaformis	Lake Whitefish	2	4	5	16	0	0
Coregonus autumnalis	Arctic Cisco	18	40	0	0	1	4
Oncorhynchus tshawytscha	Chinook Salmon	6	13	25	78	1	4
Oncorhynchus keta	Chum Salmon	1	2	7	22	3	13
Oncorhynchus kisutch	Coho Salmon	3	7	5	16	0	0
Oncorhynchus nerka	Sockeye Salmon	0	0	4	13	1	4
Oncorhynchus gorbuscha	Pink Salmon	2	4	0	0	2	8
Thymallus arcticas	Arctic Grayling	0	0	9	28	0	0
Stenodus nelma	Inconnu	24	53	1	3	17	71
Lotidae Family							
Lota Lota	Burbot	12	27	7	22	10	42
Osmeridae Family							
Thaleichthys pacificus	Eulachon	0	0	1	3	0	0
Percidae Family							
Sander vitreus	Walleye	1	2	0	0	0	0
Monodontidae Family							
Delphinapterus leucas	Beluga Whale	30	67	8	25	4	17

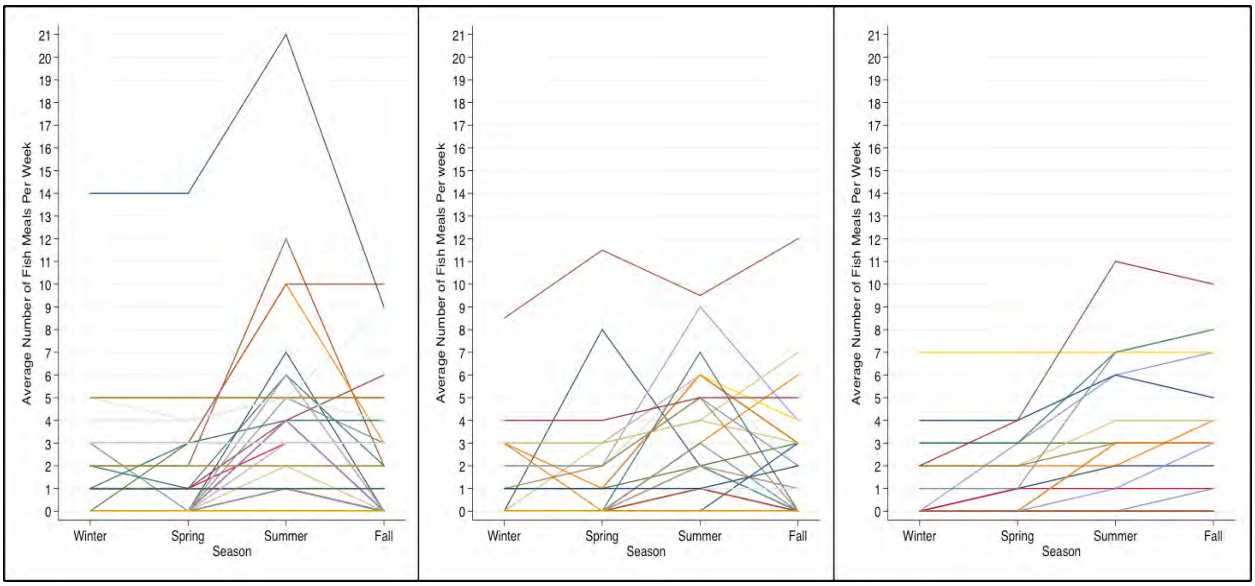
Table 19: *Five most frequent fish and marine mammal species consumed ≥1 time/week by season and community among 101 western Canadian Arctic residents, 2016*

Aklavik, NT (n=45)			Old Crow, YT (n=32)			Fort McPherson, NT (n=24)		
Species	**n**	**%**	**Species**	**n**	**%**	**Species**	**n**	**%**
Winter								
S. nelma	9	20	*C. nasus*	8	25	*C. nasus*	9	38
C. nasus	8	18	*O. tshawytscha*	6	19	*S. nelma*	5	21
D. leucas	7	16	*C. clupeaformis*	3	9			
S. malma	5	11	*O. kisutch*	2	6			
C. autumnalis	4	9	*T. arcticas*	2	6			
Spring								
S. nelma	8	18	*C. nasus*	8	25	*C. nasus*	11	46
D. leucas	8	18	*O. tshawytscha*	7	22	*S. nelma*	6	25
C. nasus	7	16	*C. clupeaformis*	4	13			
S. malma	5	11	*O. kisutch*	2	6			
C. autumnalis	4	9	*T. arcticas*	2	6			
Summer								
D. leucas	17	38	*O. tshawytscha*	20	63	*C. nasus*	14	58
S. malma	14	31	*C. nasus*	9	28	*S. nelma*	10	42
C. nasus	14	31	*O. keta*	3	9	*S. aplinus*	1	4
C. autumnalis	13	29	*S. aplinus*	2	6	*D. leucas*	1	4
S. nelma	10	22	*O. kisutch*	2	6			
			T. arcticas	2	6			
Fall								
C. nasus	9	20	*C. nasus*	9	28	*C. nasus*	15	63
S. nelma	8	18	*O. tshawytscha*	7	22	*S. nelma*	8	33
D. leucas	6	13	*O. keta*	5	16	*L. Lota*	5	21
S. malma	6	13	*L. Lota*	4	13	*S. aplinus*	1	4
C. autumnalis	4	9	*C. clupeaformis*	3	9	*S. malma*	1	4
			T. arcticas	3	9			

Hair Mercury Levels

Among participants from all communities combined, the mean concentration of MeHg in hair samples was 0.60 µg/g (SD: 0.47; Range: 0.059-2.07). This varied slightly across communities, with mean values from Aklavik, NT, Old Crow, YT and Fort McPherson, NT of 0.51 µg/g (SD: 0.44; Range: 0.06-2.07), 0.54 µg/g (SD: 0.35; Range: 0.11-1.51) and 0.84 µg/g (SD: 0.58; Range: 0.06-1.90), respectively. The distributions of MeHg in hair samples across the entire study population and stratified by community are shown in figure 15. Mean hair mercury levels (µg/g) ± SD stratified by population characteristics are shown in tables 20 and 21. No participants had hair mercury levels that exceeded the exposure maximum defined by Health Canada.

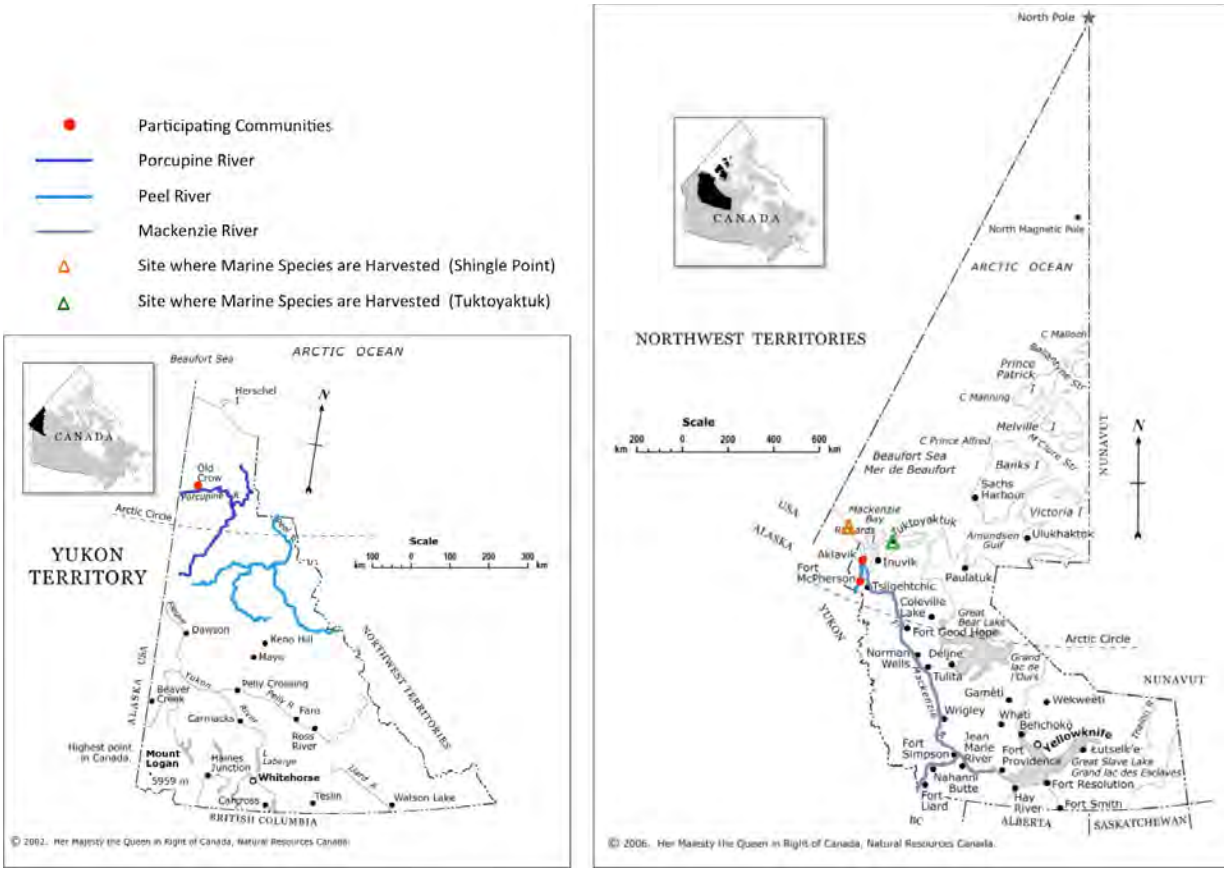
Figure 13: *Average number of fish or marine mammal meals per week by season among participants from Aklavik (Left; n=45), Old Crow (Middle; n=32) and Fort McPherson (Right; n=24), 2016. Each line represents an individual*



Relationship Between Fish & Marine Mammal Intake and MeHg in Hair

Data were insufficient to allow for estimation of species-specific effects on hair mercury levels, so this analysis was limited to effects of total fish/whale consumption. MeHg levels stratified by total fish/whale consumption frequency across different seasons are shown in table 22. The strong correlations between season-specific fish/whale consumption variables prohibited including them all in the same model, so season-specific effects were estimates in separate models. Model building procedures yielded the same set of adjustment variables for fish/whale consumption in each season: sex, hair length, use of hair dye or other permanent hair treatments, and the proportion of fish/whale meals usually prepared by cooking. There was no evidence of statistical interaction between fish/whale consumption frequency and other covariates in the model. Visual inspection of the lowess plots representing the locally weighted regression of MeHg concentration on exposure variables for each season indicated the relationships were not linear enough to justify modeling them as continuous.

Figure 14: *Maps showing the main waterways and sites from which participants harvest fish and marine mammals in the Northwest Territories and Yukon and the locations of participating communities*



There was a trend characterized by increasing MeHg concentration with increasing fish/whale consumption frequency in each of the seasons (p-values for trend ranging from <0.0001 to 0.005). Results of multivariable random effects regression analysis are shown in tables 23-26. Unadjusted estimates of the effect of fish/whale consumption frequency on hair mercury level showed consistent increases in MeHg concentration as fish intake increased in all four seasons (tables 23-26). The unadjusted estimates for fish/whale consumption in each season showed increases in MeHg concentration ranging from 0.12 to 0.3 µg/g among participants who consumed 1-2 meals/week, compared to those who consumed <1 meal/week. Similarly, hair mercury concentrations among participants who had the highest level of fish/whale consumption in each season ranged from 0.3 to 0.5 µg/g higher than those who consumed <1 meal/week. The magnitude of the effect of each consumption category decreased slightly following adjustment in all seasons (tables 23-26). The magnitude of the change in hair MeHg concentration in response to consuming ≥ 3 vs.

<1 meal/week was highest for intake during the spring (β: 0.4; 95%CI: 0.2, 0.6). Conversely, the magnitude of this effect was lowest for intake during the winter (β: 0.28; 95%CI: 0.07, 0.5). The intercepts from these models, representing the expected mean concentration of mercury (µg/g) if all covariates are at their reference level, and corresponding SDs, representing the variation in these values associated with clustering in communities, are shown in each table. These estimates show that for each model, variation in baseline hair-mercury concentrations across communities is not fully explained by the variables in the model, given residual clustering by community.

Figure 15: *Distribution of methylmercury measurements (µg/g) in hair samples among western Canadian Arctic residents by community, 2016*

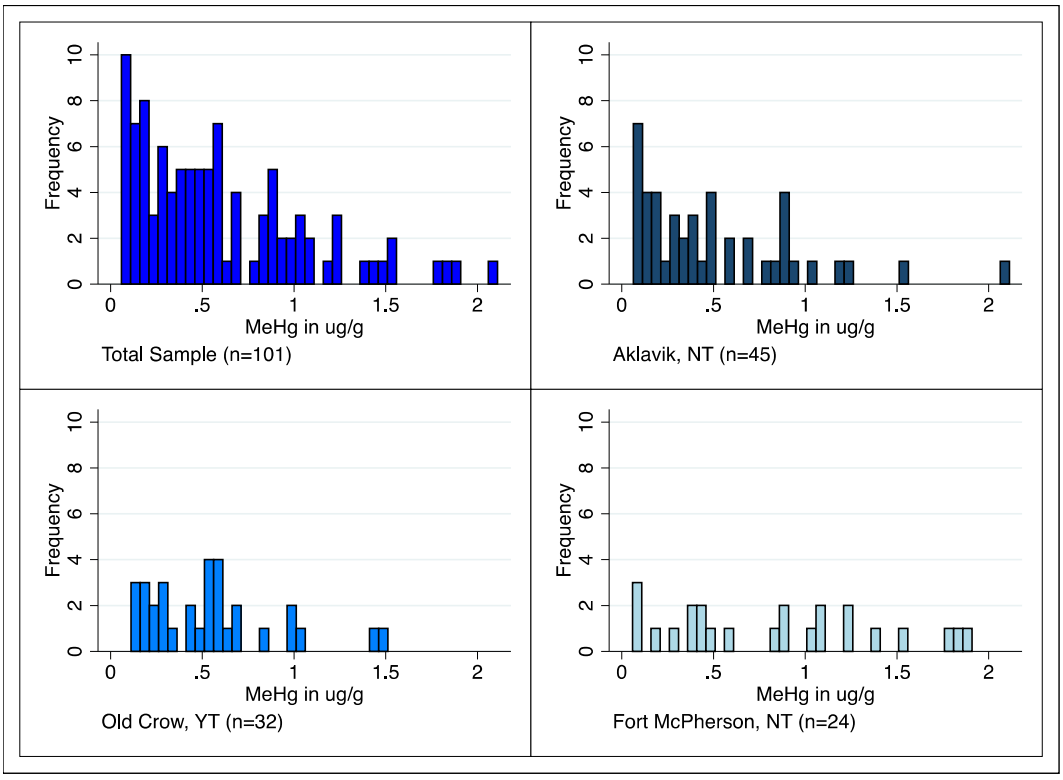


Table 20: *Distribution of demographic characteristics and stratum-specific mean methylmercury concentrations (µg/g) among participants from Aklavik, NT, Fort McPherson, NT and Old Crow YT, 2016*

Demographic Characteristics	Total (n=101)		Aklavik, NT (n=45)		Old Crow, YT (n=32)		Fort McPherson, NT (n=24)	
	n (%)	Mean ± SD	n (%)	Mean ± SD	n (%)	Mean ± SD	n (%)	Mean ± SD
Age								
≤ 30 years	9 (9)	0.26 ± 0.21	5 (11)	0.17 ± 0.08	4 (13)	0.37 ± 0.27	0 (0)	-
31-40 years	15 (15)	0.45 ± 0.60	8 (18)	0.50 ± 0.70	4 (13)	0.53 ± 0.66	3 (13)	0.20 ± 0.23
41-50 years	14 (14)	0.49 ± 0.34	8 (18)	0.41 ± 0.35	4 (13)	0.58 ± 0.35	2 (8)	0.59 ± 0.44
52-60 years	35 (35)	0.79 ± 0.52	14 (31)	0.60 ± 0.35	7 (22)	0.57 ± 0.44	14 (58)	1.09 ± 0.57
61-70 years	17 (17)	0.57 ± 0.31	6 (13)	0.78 ± 0.43	9 (28)	0.47 ± 0.16	2 (8)	0.42 ± 0.004
≥ 71 years	11 (11)	0.64 ± 0.39	4 (9)	0.42 ± 0.36	4 (13)	0.78 ± 0.27	3 (13)	0.75 ± 0.56
Sex								
Male	37 (37)	0.74 ± 0.51	13 (29)	0.53 ± 0.46	17 (53)	0.68 ± 0.40	7 (29)	1.28 ± 0.49
Female	64 (63)	0.51 ± 0.42	32 (71)	0.50 ± 0.43	15 (47)	0.38 ± 0.20	17 (71)	0.66 ± 0.52

Table 21: *Distribution of permanent hair treatment use and stratum-specific methylmercury concentrations (µg/g) among participants from Aklavik, NT, Fort McPherson, NT and Old Crow YT, 2016*

Hair Treatments	Total (n=101)		Aklavik, NT (n=45)		Old Crow, YT (n=32)		Fort McPherson, NT (n=24)	
	n (%)	Mean ± SD	n (%)	Mean ± SD	n (%)	Mean ± SD	n (%)	Mean ± SD
Dyed								
No	74 (73)	0.63 ± 0.48	33 (73)	0.48 ± 0.37	20 (63)	0.62 ± 0.40	21 (88)	0.87 ± 0.61
Yes	27 (27)	0.51 ± 0.43	12 (27)	0.59 ± 0.59	12 (38)	0.40 ± 0.21	3 (13)	0.62 ± 0.34
Perm								
No	95 (94)	0.61 ± 0.48	45 (100)	0.51 ± 0.44	31 (97)	0.55 ± 0.36	19 (79)	0.92 ± 0.61
Yes	6 (6)	0.48 ± 0.30	0 (0)	-	1 (3)	0.28	5 (21)	0.52 ± 0.31
Dye or Perm								
No	70 (69)	0.64 ± 0.49	33 (73)	0.48 ± 0.37	20 (63)	0.62 ± 0.40	17 (71)	0.95 ± 0.64
Yes	31 (31)	0.51 ± 0.42	12 (27)	0.59 ± 0.59	12 (38)	0.40 ± 0.21	7 (29)	0.58 ± 0.32

Table 22: *Distribution of fish consumption frequencies in each season and stratum-specific methylmercury concentrations (µg/g) among participants from Aklavik, NT, Fort McPherson, NT and Old Crow YT, 2016*

Intake Category	Total (n=101)		Aklavik, NWT (n=45)		Old Crow, YT (n=32)		Fort McPherson, NWT (n=24)	
	n	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**
Winter								
< 1 meal/week	55	0.51 ± 0.46	23	0.41 ± 0.39	17	0.40 ± 0.24	15	0.80 ± 0.63
1-2 meals/week	27	0.61 ± 0.38	13	0.57 ± 0.35	9	0.67 ± 0.42	5	0.62 ± 0.45
≥ 3 meals/week	19	0.82 ± 0.54	9	0.69 ± 0.61	6	0.74 ± 0.40	4	1.24 ± 0.38
Spring								
< 1 meal/week	51	0.41 ± 0.34	23	0.34 ± 0.30	16	0.37 ± 0.24	12	0.59 ± 0.48
1-2 meals/week	28	0.71 ± 0.46	12	0.57 ± 0.37	10	0.70 ± 0.41	6	1.00 ± 0.61
≥ 3 meals/week	22	0.89 ± 0.55	10	0.83 ± 0.60	6	0.71 ± 0.35	6	1.18 ± 0.59
Summer								
< 1 meal/week	28	0.44 ± 0.38	11	0.37 ± 0.33	8	0.41 ± 0.28	9	0.55 ± 0.52
1-2 meals/week	24	0.52 ± 0.49	11	0.38 ± 0.38	9	0.34 ± 0.22	4	1.34 ± 0.44
3-4 meals/week	18	0.62 ± 0.45	9	0.60 ± 0.44	4	0.42 ± 0.16	5	0.80 ± 0.62
≥ 5 meals/week	31	0.78 ± 0.48	14	0.67 ± 0.52	11	0.83 ± 0.37	6	0.96 ± 0.58
Fall								
< 1 meal/week	45	0.42 ± 0.36	23	0.37 ± 0.33	14	0.41 ± 0.26	8	0.57 ± 0.55
1-2 meals/week	17	0.59 ± 0.49	8	0.50 ± 0.35	6	0.41 ± 0.34	3	1.18 ± 0.75
3-4 meals/week	23	0.79 ± 0.47	8	0.63 ± 0.46	8	0.87 ± 0.41	7	0.89 ± 0.55
≥ 5 meals/week	16	0.83 ± 0.54	6	0.91 ± 0.65	4	0.51 ± 0.14	6	0.96 ± 0.59

Table 23: *Results of multivariable random-effects models for fish consumption frequency during the spring season among 101 western Canadian Arctic residents, 2016*

	Unadjusted		Adjusted Φ		p-value for Trend
	β	**95% CI**	**β**	**95% CI**	
Sex					
Male	*Reference*		*Reference*		
Female	-0.25	-0.43, -0.07	-0.05	-0.25, 0.14	
Hair Length (cm)	-0.01	-0.01, -0.002	-0.004	-0.01, 0.0003	
Dye or Perm					
No	*Reference*		*Reference*		
Yes	-0.12	-0.31, 0.066	-0.17	-0.33, -0.004	
Proportion Cooked	0.004	0.0001, 0.008	0.003	0.00004, 0.01	
Spring					
< 1 meal/week	*Reference*		*Reference*		
1-2 meals/week	0.30	0.12, 0.49	0.26	0.08, 0.44	
≥ 3 meals/week	0.48	0.27, 0.68	0.41	0.20, 0.61	<0.01
Random intercept for community from adjusted model: **SD 0.131 (95%CI: 0.045, 0.379)**					

Φ Model covariates: sex, hair length, use of hair dyes or permanent treatments, the proportion of fish meals usually prepared by cooking, and fish consumption frequency in the summer

Table 24: *Results of multivariable random-effects models for fish consumption frequency in the summer season among 101 western Canadian Arctic residents, 2016*

	Unadjusted		Adjusted Φ		p-value for Trend
	β	**95% CI**	**β**	**95% CI**	
Sex					
Male	*Reference*		*Reference*		
Female	-0.25	-0.43, -0.07	-0.14	-0.34, 0.05	
Hair Length (cm)	-0.01	-0.01, -0.002	-0.004	-0.01, 0.0002	
Dye or Perm					
No	*Reference*		*Reference*		
Yes	-0.12	-0.31, 0.066	-0.157	-0.33, 0.019	
Proportion Cooked	0.004	0.0001, 0.008	0.004	0.001, 0.01	
Summer					
< 1 meal/week	*Reference*		*Reference*		
1-2 meals/week	0.12	-0.11, 0.35	0.04	-0.18, 0.27	
3-4 meals/week	0.19	-0.07, 0.59	0.18	-0.07, 0.43	
≥ 5 meals/week	0.37	0.16, 0.59	0.32	0.11, 0.53	<0.01
Random intercept for community from adjusted model: **SD 0.147 (95%CI: 0.053, 0.409)**					

Φ Model covariates: sex, hair length, use of hair dyes or permanent treatments, the proportion of fish meals usually prepared by cooking, and fish consumption frequency in the summer

Table 25: *Results of multivariable random-effects models for fish consumption frequency during the fall season among 101 western Canadian Arctic residents, 2016*

	Unadjusted		Adjusted Φ		p-value for Trend
	β	**95% CI**	**β**	**95% CI**	
Sex					
Male	*Reference*		*Reference*		
Female	-0.25	-0.43, -0.07	-0.09	-0.29, 0.11	
Hair Length (cm)	-0.01	-0.01, -0.002	-0.004	-0.01, 0.001	
Dye or Perm					
No	*Reference*		*Reference*		
Yes	-0.12	-0.314, 0.07	-0.22	-0.39, -0.05	
Proportion Cooked	0.004	0.0001, 0.008	0.004	0.0002, 0.01	
Fall					
< 1 meal/week	*Reference*		*Reference*		
1-2 meals/week	0.17	-0.07, 0.41	0.15	-0.07, 0.37	
3-4 meals/week	0.36	0.14, 0.57	0.32	0.11, 0.53	
≥ 5 meals/week	0.39	0.14, 0.63	0.38	0.14, 0.61	<0.01
Random intercept for community from adjusted model: **SD 0.097 (95%CI: 0.025, 0.369)**					
Φ Model covariates: sex, hair length, use of hair dyes or permanent treatments, the proportion of fish meals usually prepared by cooking, and fish consumption frequency in the fall					

Table 26: *Results of multivariable random-effects models for fish consumption frequency in the winter season among 101 western Canadian Arctic residents, 2016*

	Unadjusted		Adjusted Φ		p-value for Trend
	β	**95% CI**	**β**	**95% CI**	
Sex					
Male	*Reference*		*Reference*		
Female	-0.25	-0.43, -0.07	-0.13	-0.33, 0.07	
Hair Length (cm)	-0.01	-0.01, -0.002	-0.004	-0.01, 0.0004	
Dye or Perm					
No	*Reference*		*Reference*		
Yes	-0.12	-0.31, 0.07	-0.17	-0.34, 0.01	
Proportion Cooked	0.004	0.0001, 0.008	0.004	0.001, 0.01	
Winter					
< 1 meal/week	*Reference*		*Reference*		
1-2 meals/week	0.12	-0.08, 0.32	0.11	-0.08, 0.30	
≥ 3 meals/week	0.33	0.10, 0.55	0.28	0.07, 0.50	<0.01
Random intercept for community from adjusted model: **SD 0.143 (95%CI: 0.050, 0.405)**					
Φ Model covariates: sex, hair length, use of hair dyes or permanent treatments, the proportion of fish meals usually prepared by cooking, and fish consumption frequency in the winter					

Other Dietary Components

The distribution of fruit and vegetable consumption did not range widely across study participants (table 27). Conversely, a large proportion of participants reported consuming dairy products more than once per day (45%; 45/101). Of 101 participants, 40 reported the regular use of dietary supplements. Of these, 77.5% (31/40) took vitamins, 27.5% (11/40) took calcium, 10% (4/40) took fish oil, 10% (4/10) took omega-3 and 7.5% (3/40) took dietary fibre. MeHg concentrations stratified by categories of consumption frequency for these dietary components and use of dietary supplements are shown in table 27. Inspection of these distributions does not reveal any patterns of association between intake frequencies and hair MeHg levels. This is consistent with the results of the model building procedures, which did not yield evidence that these dietary factors act as important confounders or effect-measure modifiers in the relationship between fish/whale consumption frequency and hair MeHg concentration in this population. However, given the power required to detect these relationships in a statistical model, this finding could reflect insufficient data for proper estimation of these effects.

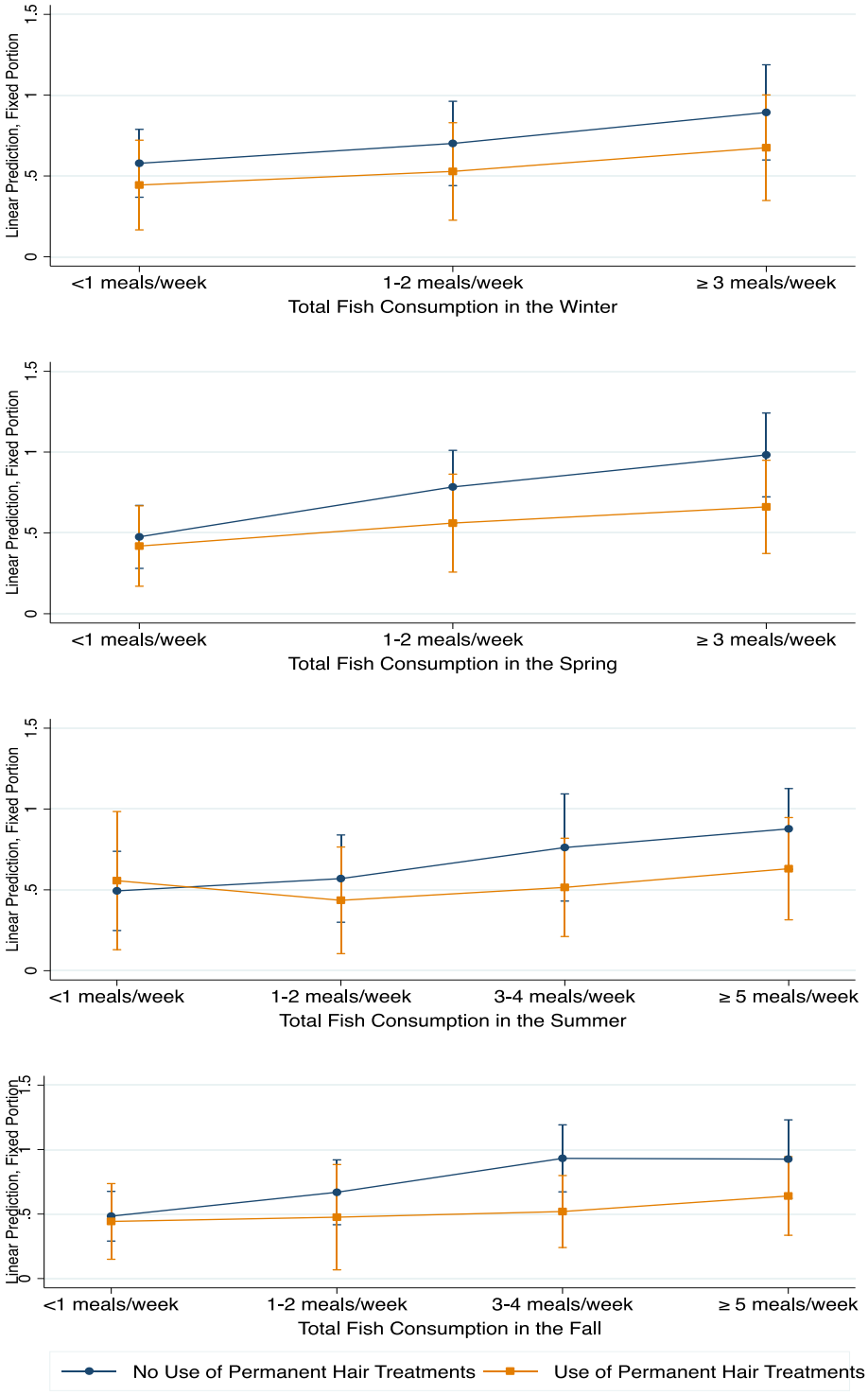
Characteristics of Hair

Hair length was inversely correlated with MeHg concentration, with 1 cm increases in length corresponding to slight reductions in average µg/g of mercury after adjusting for sex, permanent hair treatment use, fish/whale consumption frequency and the proportion of fish/whale meals prepared by cooking (tables 23-26). Multivariable random effects regression models yielded evidence of a reduction in hair mercury concentration among those who reported recent use of permanent hair treatments, relative to those with untreated hair (tables 23-26). Figure 16 shows the adjusted effects of consuming different quantities of fish/whale in each season on hair mercury concentration, stratified by use of permanent hair treatments. These graphs show that within the same categories of fish/whale intake, participants who used permanent hair treatments had lower hair mercury concentrations, relative to those who did not.

Table 27: *Distribution of intake frequencies and other dietary components and stratum-specific methylmercury concentrations (µg/g) among 101 western Canadian Arctic residents, 2016*

	Total (N=101)		Aklavik, NWT (N=45)		Old Crow, YT (N=32)		Fort McPherson, NWT (N=24)	
	n (%)	**Mean ± SD**	**n (%)**	**Mean ± SD**	**n (%)**	**Mean ± SD**	**n (%)**	**Mean ± SD**
Fruit & Vegetables								
1-3 times/week	20 (20)	0.69 ± 0.52	11 (24)	0.53 ± 0.42	5 (16)	0.48 ± 0.18	4 (17)	1.39 ± 0.49
4-7 times/week	27 (27)	0.61 ± 0.51	12 (27)	0.49 ± 0.39	5 (16)	0.51 ± 0.44	10 (42)	0.81 ± 0.64
> 1 time/day; < 2 times/day	30 (30)	0.53 ± 0.40	13 (29)	0.36 ± 0.28	11 (34)	0.67 ± 0.44	6 (25)	0.65 ± 0.45
≥ 2 times/day	24 (24)	0.59 ± 0.47	9 (20)	0.74 ± 0.63	11 (34)	0.45 ± 0.27	4 (17)	0.64 ± 0.51
Dairy								
≤ 1 time/week	29 (29)	0.61 ± 0.50	13 (29)	0.53 ± 0.40	10 (31)	0.50 ± 0.43	6 (25)	0.96 ± 0.72
2-4 times/week	14 (14)	0.67 ± 0.42	9 (20)	0.59 ± 0.40	1 (3)	0.59	4 (17)	0.88 ± 0.50
5-7 times/week	13 (13)	0.25 ± 0.16	9 (20)	0.23 ± 0.13	2 (6)	0.37 ± 0.25	2 (8)	0.23 ± 0.24
> 1 time/day	45 (45)	0.67 ± 0.49	14 (31)	0.62 ± 0.56	19 (59)	0.57 ± 0.34	12 (50)	0.86 ± 0.57
Uses Dietary Supplements								
No	62 (61)	0.58 ± 0.47	33 (73)	0.46 ± 0.36	19 (59)	0.59 ± 0.44	10 (42)	0.94 ± 0.66
Yes	39 (39)	0.63 ± 0.47	12 (27)	0.66 ± 0.59	13 (41)	0.46 ± 0.16	14 (58)	0.77 ± 0.54

Figure 16: *Hair-methylmercury levels (µg/g) for different categories of fish consumption frequency stratified by use of permanent hair treatments, adjusted for sex, proportion of fish meals usually prepared by cooking and hair length*



Community Effect

SDs and corresponding 95%CIs representing the random effect for clustering in communities are presented in tables 23-26. Visual comparison of community-specific patterns of fish/whale intake (table 19) revealed the following species as those most likely to discriminate between communities based on the relative frequencies of their use: Beluga Whale (*D.leucas*), Arctic Grayling (*T.arcticas*), Chinook Salmon (*O.tshawytscha*) and Burbot (*L.lota*). Assessment of the linearity of the relationships between frequency of consuming each of these species and MeHg concentration in hair indicated these variables could be modeled as continuous. The SDs and 95%CIs representing residual variation across communities when new species were added as covariates to the model are shown in table (28). The largest reduction in the magnitude of the SD was in the fall model, with the addition of continuous variables representing intake of Chinook Salmon (*O.tshawytscha*) and Arctic Grayling (*T.arcticas*) in the fall. Variation across communities increased with the inclusion of beluga whale consumption for all models to which it was added (table 28), likely because whale consumption was almost exclusively reported by residents of Aklavik, NT. Inclusion of this variable highlighted a strong association between Beluga Whale (*D.leucas*) consumption and hair MeHg concentration. The beta coefficients (95%CI) for each one-meal increase in weekly consumption of beluga whale in the spring, summer, fall and winter seasons were 0.2 (0.01, 0.4), 0.04 (-0.05, 0.1), 0.3 (0.05, 0.5) and 0.3 (-0.04, 0.6), respectively.

Bias Analysis

The laboratory technicians randomly selected 22 samples for duplicate MeHg concentration measurement. Of these, 4 were obtained from the same individuals randomly selected by EVW as blind duplicates (n=10), yielding a total of 28 participants on which duplicate measurements were made. Excluding one outlier, the mean percent change in MeHg concentration between measurements was 15.84% (SD: 9.95; Range: 3.32 - 43.77). The participant with a percent change in repeated measurements falling well outside the range of other values was a female, with hair that had been dyed approximately one month prior to the date of sample collection. The percent change between repeated measurements of this participant's hair sample was 159%. Among all 28 individuals on which duplicate measurements were made, the median percent change in MeHg concentration between measurements was 14.67% (IQR: 10.75).

Table 28: *Sensitivity analysis of factors associated with residual between-community heterogeneity among 101 western Canadian Arctic residents, 2016*

Model	SD	95%CI
Spring		
Model 1: **Sex, Hair Length, Proportion Cooked, Permanent Hair Treatments, Total Fish Consumption in the Spring**	0.131	0.045, 0.379
Model 1 **+ Beluga Whale Consumption**	0.144	0.053, 0.393
Model 1 **+ Arctic Grayling Consumption**	0.124	0.042, 0.370
Model 1 **+ Chinook Salmon Consumption**	0.116	0.037, 0.363
Model 1 **+ Chinook Salmon & Arctic Grayling Consumption**	0.115	0.037, 0.361
Summer		
Model 2: **Sex, Hair Length, Proportion Cooked, Permanent Hair Treatments, Total Fish Consumption in the Summer**	0.156	0.057, 0.423
Model 2 **+ Beluga Whale Consumption**	0.159	0.059, 0.426
Model 2 **+ Chinook Salmon Consumption**	0.155	0.054, 0.445
Model 2 **+ Arctic Grayling Consumption**	0.150	0.054, 0.413
Model 2 **+ Chinook Salmon & Arctic Grayling Consumption**	0.154	0.054, 0.442
Fall		
Model 3: **Sex, Hair Length, Proportion Cooked, Permanent Hair Treatments, Total Fish Consumption in the Fall**	0.105	0.030, 0.371
Model 3 **+ Burbot Consumption**	0.109	0.032, 0.371
Model 3 **+ Beluga Whale Consumption**	0.119	0.038, 0.368
Model 3 **+ Arctic Grayling Consumption**	0.092	0.022, 0.382
Model 3 **+ Chinook Salmon Consumption**	0.070	0.010, 0.473
Model 3 **+ Chinook Salmon & Arctic Grayling Consumption**	0.064	0.008, 0.534
Winter		
Model 4: **Sex, Hair Length, Proportion Cooked, Permanent Hair Treatments, Total Fish Consumption in the Winter**	0.151	0.054, 0.417
Model 4 **+ Burbot Consumption**	0.146	0.052, 0.411
Model 4 **+ Arctic Grayling Consumption**	0.146	0.052, 0.410
Model 4 **+ Chinook Salmon Consumption**	0.140	0.048, 0.404
Model 4 **+ Chinook Salmon & Arctic Grayling Consumption**	0.139	0.048, 0.403
Model 4 **+ Chinook Salmon, Arctic Grayling & Burbot Consumption**	0.133	0.045, 0.394

Among 28 participants with repeat measurements of MeHg concentration, 36% (10/28) had values that increased. Therefore the MeHg concentration for a random selection of 36% of the study population was increased by the mean percent change excluding the outlier (15.84%). The MeHg concentrations for the remaining 64% of the study population decreased by 15.84%. If these adjusted values represented the true distribution of MeHg concentrations in the sample, the mean would be 0.58 µg/g (SD: 0.47; Range: 0.05-2.05).

EVW inspected the distribution of mean percent change in measurements across participant characteristics and identified use of hair dyes or permanent hair treatments as possibly related to the magnitude of the difference between repeated measurements. The mean percent change between measurements among those who reported recent use of hair dye or other permanent hair treatments was 38.5 (SD: 59.5), compared to 16.2 (SD: 10.4) among those who did not. Among those who used permanent hair treatments, 50% had values that increased across measurements. Among those without permanent hair treatment, 32% had values that increased across measurements. When MeHg concentrations of a random selection of participants stratified by hair treatment status were increased or decreased by the stratum-specific mean percent change, the population mean became 0.57 μg/g (SD: 0.50; Range: 0.05-2.87). Under each of these scenarios, all participants remained at levels below those thought to pose serious health risks. Table 29 shows results of regression models using as outcomes the originally measured MeHg concentration, and alternately, the values adjusted for measurement error. These comparisons indicate that error in laboratory measurement of MeHg is not likely to have impacted inferences drawn from this analysis.

Table 29: *Results of multivariable random-effects models using the originally measured methylmercury value and adjusted values based on the magnitude of change among 28 individuals with repeat measurements*

Fish/Whale Intake (Meals/Week)	Original MeHg Measurement			Adjusted MeHg Measurement 1 ⌘			Adjusted MeHg Measurement 2§		
	β	**95% CI**	**p for Trend**	**β**	**95% CI**	**p for Trend**	**β**	**95% CI**	**p for Trend**
Spring									
< 1	*Reference*			*Reference*			*Reference*		
1-2	0.26	0.08, 0.44		0.23	0.05, 0.41		0.29	0.09, 0.49	
≥ 3	0.41	0.20, 0.61	0.000	0.38	0.17, 0.58	0.000	0.44	0.22, 0.67	0.000
Summer									
< 1	*Reference*			*Reference*			*Reference*		
1-2	0.04	-0.18, 0.27		0.02	-0.21, 0.24		0.08	-0.17, 0.33	
3-4	0.18	-0.07, 0.43		0.10	-0.13, 0.34		0.06	-0.20, 0.32	
≥ 5	0.32	0.11, 0.53	0.001	0.29	0.09, 0.50	0.001	0.37	0.14, 0.59	0.001
Fall									
< 1	*Reference*			*Reference*			*Reference*		
1-2	0.15	-0.07, 0.37		0.14	-0.09, 0.36		0.19	-0.06, 0.43	
3-4	0.32	0.11, 0.53		0.22	0.01, 0.43		0.18	-0.053, 0.41	
≥ 5	0.38	0.14, 0.61	0.000	0.27	0.04, 0.51	0.000	0.40	0.14, 0.66	0.000
Winter									
< 1	*Reference*			*Reference*			*Reference*		
1-2	0.11	-0.08, 0.30		0.09	-0.10, 0.27		0.11	-0.10, 0.32	
≥ 3	0.28	0.07, 0.50	0.005	0.29	0.08, 0.50	0.004	0.30	0.07, 0.54	0.008

⌘ MeHg concentrations adjusted by the mean percent change estimated among 27 individuals with repeat measurements of 15.8% (excluding 1 outlier). MeHg concentration was increased for a Random selection of 36% of participants and decreased for the remaining 64%.

§ MeHg concentrations adjusted according to reported use of permanent hair treatments. The mean percent change among 6 participants with reported use of permanent hair treatments (38.5%) and among 22 participants without use of permanent hair treatments (16.17%) was used to adjust the concentration. Among those who used hair treatments, 50% were increased by 38.5%. Among those who did not use permanent hair treatments, 32% were increased by 16.2%.

Discussion

Overall, the level of MeHg measured in hair samples obtained from participants was low; all well below the cut point under which no serious health effects associated with MeHg are expected [230]. Participants in this study reported consuming a wide variety of fish species, the frequency of which varied by season and community. In each season, increasing fish/whale consumption frequency in each season was associated with increasing MeHg concentration in hair. Variation across communities was partially explained by the specific types of fish consumed, with Chinook Salmon (*O.tshawytscha*) and Arctic Grayling (*T.arcticas*) reducing the amount of residual heterogeneity measured in multivariable random effects models. Further, consumption of Beluga Whale (*D.leucas*) was strongly associated with increased hair-mercury concentration. These analyses highlighted use of permanent hair treatments as important factors influencing measurements of MeHg concentration. However, data were insufficient for precise estimation of this effect.

These findings are consistent with the literature pertaining to the relationship between fish and marine mammal intake and internal dose of mercury as measured in hair [104,105,107–109,112,115–117,119,122–129,131,134,136,139–141,145,147,149,152,154–156,158,159,161,164,165,167–171]. Among studies included in the systematic review in chapter 1 of this dissertation, increasing fish consumption was associated with increasing hair mercury concentrations in 66% (44/67). Additionally, the nonlinear shape of this relationship among participants of the present study is not unexpected. Findings from the systematic review showed that the shape of the relationship between fish consumption frequency and hair mercury level was not exclusively linear and varied across populations. Finally, results of the investigation into factors associated with the magnitude of the difference in hair-mercury level between repeated analyses are consistent with the existing body of literature. Specifically, this analysis highlighted the use of dyes and other permanent hair treatments as being associated with the greatest percent-change between repeated measurements. This is concordant with evidence suggesting cuticle damage impacts the retention of compounds, given the potential for treatment induced damage to differentially impact strands within the same region of the head [233]. Future research should further investigate the potential for hair treatments to differentially impact strands in the same region of the head and subsequent reliability of biomarker measurements in hair.

These analyses were limited by insufficient data for precise estimation of some effects of interest on hair mercury levels. In particular, this research would have benefited from assessment of the relative impact of all individual species that participants reported consuming. Additionally, more statistical power would aid in the investigation of the potential for other dietary factors to act as effect-measure modifiers in the relationship between fish consumption and hair mercury level. Finally, results indicated that use of permanent hair treatments was associated with greater percent-change in repeated measurements of the same individual's sample. However, this finding must be interpreted with caution because of the small number of repeated analyses conducted on samples from participants who used permanent hair treatments (n=6). Other sources of variation, including laboratory error, cannot be ruled out.

Hair length was inversely correlated with MeHg concentration, after adjusting for other participant characteristics. Because samples were collected in the fall, this finding may reflect seasonal variation in fish/whale consumption among participants, characterized by more frequent intake during the summer months (figure 13). If the overall concentration measured in longer hair incorporates time periods during which consumption was less frequent, this would contribute to lower average measurements, relative to participants with shorter hair that grew exclusively during months with more frequent exposure. Additionally, there was a wide range of hair lengths among the collected samples, representing diverse exposure periods (median: 1.1 years; IQR: 2.1 years). This could have impacted the comparability across samples obtained from participants whose hair had been growing for different periods of time. Although hair length was included as a covariate in multivariable regression models, this may not have adequately controlled for the differential relationship between hair of various lengths and fish consumption in each of the seasons. Further, it has been suggested that the exposure time windows represented in hair samples should be interpreted with caution, given the potential for hair growth rates to vary across individuals [92,207]. For this reason, an expert panel convened by the U.S Agency for Toxic Substances and Disease Registry (ATSDR) to review the state of the science pertaining to hair analysis concluded that exposures occurring close to the time at which samples are collected or those occurring more than 1 year prior to collection may not be reliably represented in the hair sample for all members of a study population [92,207]. An additional consideration is the extent to which measurements in distal ends of strands that have been growing for extended periods of time can be considered reliable. Although MeHg remains chemically stable in hair

relative to other tissues, a proportion of MeHg deposited in hair may be released over time, particularly if the cuticle sustains damage [92,207,233].

A major strength of this research is the close partnership and collaboration with members of participating Indigenous communities. Local planning committees provided information on key aspects of fish consumption practices among community members. Input from planning committees improved the accuracy of the collected data, by informing the development of the fish-focussed FFQ and timing of hair sample collection. In particular, this allowed the incorporation of commonly used names for different species, which likely improved participants' ability to provide accurate responses. This is evident in the consistency between results of these analyses and the existing body of evidence on fish and marine mammal consumption and measurements of mercury in hair. For example, the strong association between Beluga Whale (*D.leucas*) consumption and MeHg is expected, given the likely degree of contamination in large marine mammals [211,234].

Conclusions

This mercury exposure project highlighted that a large proportion of participants from selected western Canadian Arctic communities regularly consume a wide range of fish species. Fish consumption frequency in each season was associated with increases in hair MeHg concentrations. However overall, MeHg concentrations measured in the collected hair samples were low, indicating that fish consumption practices among participants are not placing them at an elevated risk of serious health outcomes associated with exposure based on known mercury effects.

Chapter 4: Community-Driven Research in the Canadian Arctic: Investigating the Effect of Dietary Exposure to Mercury on Gastric Health Outcomes

Introduction

Gastritis is a pathological condition characterized by inflammation of the gastric mucosa, which is triggered by injury to the gastric epithelial cells [11,12]. Gastritis may be acute or chronic, depending on which factors contributed to its development and the duration of exposure to these factors [11–13]. Inflammation of the gastric mucosa displays a spectrum of severity; the determinants of severity are poorly understood. Chronic gastritis is a known risk factor for the development of serious digestive diseases, including peptic ulcer disease and gastric cancer [235–237]. In a widely accepted model of gastric carcinogenesis, lesions that follow chronic gastritis and indicate increased risk of carcinoma include gastric atrophy and intestinal metaplasia of the gastric mucosa [7–10]. Gastric atrophy refers to the deterioration of gastric glands [7–10,13]. Intestinal metaplasia signifies a continuum of changes, characterized by the replacement of atrophied gastric glands with phenotypically intestinal epithelium [7–10,12,13].

Five broad categories of known causes of the gastric mucosal cell injury lead to gastritis: biological agents; exogenous and endogenous chemicals; hypoxia and ischemia; physical factors; and genetic abnormalities [11–13]. The most common known cause of chronic gastritis is persistent infection with *Helicobacter pylori,* bacteria that colonize the stomach and/or duodenum [11–13]. This infection is found in populations around the globe, though the frequency varies across regions [47–50]. Community-driven projects conducted by the Canadian North *Helicobacter pylori* (CAN*Help*) Working Group have demonstrated higher prevalence of severe gastritis in Indigenous communities in Arctic Canada compared to *H.pylori*-positive members of a southern Canadian urban population [36]. The factors associated with this increased prevalence of gastritis are not clear. Exposure to exogenous chemicals is a major concern in northern communities, due to awareness of the vulnerability of Arctic ecosystems to contaminants. Before designing the research presented in this report, EVW conducted semi-structured interviews with key-informants from participating communities to ensure their concerns were addressed (unpublished data). Most respondents expressed concern about environmental contaminants, particularly mercury (Hg), affecting digestive health. Participants relayed the view that since residents of Arctic communities follow a subsistence

lifestyle, they are uniquely vulnerable to contamination of local water sources and aquatic or land animals, on which they rely for their traditional diet. They expressed a high level of anxiety arising from their dependence on the natural environment coupled with the perception that they are unable to protect their ecosystem from processes that lead to the release of pollutants.

Review of the literature on Hg contamination in the Arctic, Hg toxicity and mechanisms of gastric mucosal injury indicates that community concerns are warranted [11,30–35]. However, there has been little epidemiologic investigation of the effect of chronic Hg exposure on gastric disease. This research investigates the hypothesis that chronic ingestion of low doses of Hg through fish and marine mammal consumption influences the severity of chronic gastritis and the occurrence of precancerous gastric lesions among *H.pylori*-positive residents of Indigenous Canadian Arctic communities.

Methods

Study Design

This research constituted an environmental health component of on-going community-driven projects led by the CAN*Help* Working Group in western Canadian Arctic communities. This research program established community projects guided by local planning committees at the request of community leaders. This cross-sectional analysis uses data collected at baseline from the first 3 CAN*Help* Working Group projects. The first project was launched in Aklavik, NT in 2007 (2006 census population=590; 92% identifying as Inuvialuit [Inuit] or Gwich'in [Athabascan First Nations]) [16,17]. Subsequent projects were launched in Old Crow, YT in 2010 (2011 census population= 245; ~85% identifying as Gwich'in) [19,22], and in 2012 in Fort McPherson, NT (2011 census population=844; ~90% identifying as Gwich'in) [25].

Outcome Ascertainment

Participants aged 15 years or older (and younger participants at parents' request) were offered upper gastrointestinal endoscopy with gastric biopsy, regardless of *H.pylori* infection status or history of dyspeptic symptoms, in Aklavik in February 2008, Old Crow in January 2012 and Fort McPherson in March 2013. A temporary endoscopy unit was set up in each community health center staffed by a medical team from the University of Alberta, that performed trans-nasal (Aklavik) or trans-oral (Old Crow, Fort McPherson) endoscopies for consenting participants [238], taking 7 biopsies obtained from each participant (5 for histopathology and 2 for microbiology), with pre-determined biopsy sites based on the

Updated Sydney Protocol [46]. Any visible lesions were also biopsied for pathological examination. A single pathologist specializing in gastric pathology graded the severity of acute gastritis, chronic gastritis, atrophy and intestinal metaplasia in each of 5 or more biopsies using the updated Sydney System, with scores corresponding to ordinal categories of none, mild, moderate and severe [46]. Given that acute gastritis is characterized by a shorter duration and therefore greater variability in the prevalence of acute gastritis over time, this outcome was not included in the present analysis [46]. This analysis used the highest level of severity among biopsies examined for each participant to classify the severity of each pathological outcome (table 30). The low prevalence of chronic gastritis graded as absent or mild necessitated combining those categories with gastritis graded as moderate, creating a dichotomous outcome variable comparing severe with none/mild/moderate chronic gastritis. Similarly, the low prevalence of gastric atrophy and intestinal metaplasia graded as mild, moderate or severe led to dichotomous variables representing presence versus absence of each of these pathology outcomes (table 30).

Table 30: *Severity distribution of gastric pathology outcomes among participants included in this analysis (n=80) and among all participants with gastric biopsies evaluated from all 3 community projects (n=289)*

	Participants Included in this Analysis n (%)			All Participants with Biopsies Evaluated n (%)		
Severity	**Severe Chronic Gastritis**	**Gastric Atrophy**	**Intestinal Metaplasia**	**Severe Chronic Gastritis**	**Gastric Atrophy**	**Intestinal Metaplasia**
None	8 (10)	57 (71)	66 (83)	73 (25)	204 (71)	251 (87)
Mild	7 (9)	18 (23)	10 (12)	26 (9)	60 (21)	26 (9)
Moderate	35 (44)	4 (5)	4 (5)	92 (32)	22 (8)	9 (3)
Severe	30 (38)	1 (1)	0 (0)	98 (34)	3 (1)	3 (1)

Exposure Ascertainment

Measurement of Hg exposure was not within the originally defined scope of the community projects, and was not, therefore, done at baseline when histopathology was examined. To investigate the effect of Hg exposure on gastric health, this investigation used data on exposure during a later time period as a proxy for exposure during a more etiologically relevant time period. Abundant evidence in the literature indicates that individual Hg concentrations are higher among those who regularly participate in subsistence or recreational fishing [63,64,66–71]. For this reason, evaluation of human exposure to Hg often involves characterization of fish consumption patterns [63,64,66–71]. Evidence has shown that

food frequency questionnaires (FFQ) are the optimal approach for collecting data on average long-term diet, defined as intake over months or years [28,86]. Validation studies have shown high correlations between dietary measurements taken annually over a period of several years [28,86]. Since the goal of exposure assessment for this research was to reconstruct dietary intake from several years before, EVW developed an FFQ focused on long-term average intake of fish, fish products and marine mammals to obtain more detailed intake data on these foods than was collected by a more general FFQ at baseline. This FFQ measured consumption frequencies as average number of meals of each type of fish or marine mammal per week. Data on portion size was not collected, as validation studies have shown that inclusion of this information does not substantially improve overall characterization of diet, due to poor recall [28]. Participants were asked to specify the time of year in which they typically harvest each type of fish or marine mammal, in order to account for seasonal variation in consumption.

In addition to collecting data on dietary intake of food items related to Hg exposure, EVW collected hair samples for laboratory measurement of Hg concentration, using procedures for collection and transportation of these samples outlined by the U.S Centers for Disease Control (CDC) for use in the National Health and Nutrition Examination Survey (NHANES) [225]. The form of Hg selected for analysis was methylmercury (MeHg), an organic compound that is known to bioaccumulate in the tissues of fish and marine mammals [32,33,63–65]. The advantage of this approach in addition to collecting FFQ data is that it allows direct measurement of the internal dose of MeHg, accounting for inter-individual variation in rates of metabolism and excretion [82,85]. Further, biochemical measurement of MeHg in human tissues does not require the same assumptions about consistency in Hg content of food items or accuracy of FFQ data [82,85]. The collected samples were analyzed by the University of Alberta Biogeochemical Analytical Service Laboratory (BASL), accredited by the Canadian Association for Laboratory Accreditation (CALA) as meeting ISO/IEC 17025 standards. This laboratory measured MeHg using gas chromatography inductively coupled plasma-mass spectrometry (GC-ICP-MS) [226,227]. Among samples on which repeated measurements were taken for QA/QC purposes, the magnitude of the percent change in values varied widely (median: 14.67%; IQR: 10.75) (chapter 3 of this dissertation). EVW inspected the distribution of mean percent change between measurements across outcome categories to assess whether exposure misclassification was differential or non-differential and therefore the likely direction of bias due to exposure misclassification. Additionally, she used a t-test to assess the extent to which the mean percent change differed across outcome categories.

Biochemical exposure assessment was not feasible for all participants with outcome data. To estimate mercury exposure in participants without hair samples, EVW used a predictive model based on dietary intake of relevant food items. At total of 101 participants provided detailed fish consumption data and hair samples for biochemical measurement of MeHg concentration. Data obtained from these participants permitted the development of a multivariable linear regression model to predict the mean of hair MeHg concentration from the following set of variables: sex; hair length; use of dyes or other permanent hair treatments; and total fish consumption in the summer. To assess the predictive power of the multivariable random-effects linear regression model, EVW conducted a 10-fold cross-validation analysis. To achieve this, the dataset was divided into even groups of 10. Apportionment of participants into groups was random within communities, to ensure representation of each community in every group. The model was run 10 times, each time leaving 1 of the groups out of the analysis and predicting the hair MeHg concentration in the group that was not included in that model.

Statistical Analysis

The statistical analyses aimed to estimate the association between predicted/actual hair MeHg level and the prevalence of each of the pathological outcomes: severe gastritis, atrophy and intestinal metaplasia. EVW fit a separate multivariable logistic regression model for each of these outcomes, to estimate prevalence odds ratios (OR) and 95% confidence intervals (CI) for the effect of MeHg concentration in hair on the prevalence of severe gastritis, atrophy and intestinal metaplasia. Additionally, generalized ordinal logistic regression was used to estimate ORs and 95%CIs for the effect of hair-MeHg concentration on progression from chronic inflammation to gastric atrophy and intestinal metaplasia. For this analysis, the outcome status of each participant was defined according to the most advanced pathology graded in their biopsies. The parallel regression assumption was tested using the Brant test [239]. If this assumption was violated for any of the covariates, a partial-parallel model was fit, allowing the slope of some covariates to vary across levels of the outcome [239].

Purposeful selection, as proposed by Hosmer and Lemeshow (2000), was used to identify important adjustment variables for valid estimation of the relationship between hair MeHg level and each of the pathological outcomes [240]. Variables considered for inclusion in the model were: age, sex, ethnicity, alcohol consumption, cigarette smoking, and fruit and

vegetable intake. According to Willet's Nutritional Epidemiology text, the respective strengths and weaknesses of measuring specific compounds contained in a food item and intake of whole food items warrant combining these exposure classifications in modeling exposure effects [28]. For this reason, frequency of consuming fish was included in each model in addition to hair MeHg concentrations. Inclusion of total fish consumption may also mitigate confounding by other nutrients or chemicals found in fish [28]. The LR test was used to assess the presence of interactions between MeHg concentration in hair and other variables in the model.

Since residents of the same community cannot be assumed to be independent with respect to odds of developing the disease outcomes, the inclusion of a random intercept was tested for each model. The Likelihood Ratio (LR) test was used to determine whether the magnitude of the unexplained effect of clustering in communities was large enough to require including the random effect in the final model. Alternatively, community was modeled as a fixed effect and in the absence of a confounding effect of community, robust standard errors (SE) were estimated to improve the accuracy of the SEs in the presence of clustering. Sensitivity analysis assessed the model fit and the extent to which modeling decisions impacted inferences drawn from the analyses [86]. Specifically, separate models using different versions of each variable were fit. Model results were compared to assess whether the direction, magnitude and precision of the adjusted effect estimates varied in response to changes in modeling decisions. Optimal approaches for modeling each variable were defined as those that permitted scientifically meaningful exposure contrasts, with a reasonable degree of precision. The likelihood-ratio test was used to compare the overall fit of models using different variable formats.

Estimated Intake of Selenium and Mercury

Selenium (Se) is an antioxidant and essential nutrient. Intake of Se has been shown to modify the toxicity of Hg, by bonding competitively with Hg compounds and rendering them toxicologically inert [63,69,200–204]. The complex relationship between Se and MeHg has been the focus of a large body of research aiming to better understand the risks associated with regularly consuming fish and marine mammals [63,69,200–204]. Review of this evidence highlighted the potential for Se to act as both a confounder and an effect-measure modifier in the relationship between MeHg and various toxic endpoints [63,69,200–204]. Logistic constraints prevented biochemical measurement of Se status in tissue samples provided by participants. For this reason, Se intake was approximated using FFQ data and estimates of the Se concentration in the species of fish consumed by participants. Estimates of Se

concentrations in fish tissues were obtained from published literature summarizing research on the Hg and Se concentrations in the fish and marine mammal species from the Canadian Arctic that participants reported consuming [241–245]. EVW calculated weighted mean concentrations (µg/g) for the same species measured in multiple studies (table 31) [241–245]. According to the Canadian Food Guide, one serving of cooked fish is approximately 75g [246]. Therefore, species-specific Se concentrations (µg/g) were multiplied by 75g to reflect the intake of Se per meal. Species-specific Se intake per meal was then multiplied by the number of times the participant reported consuming each species per week in each season. Total Se intake from all species combined in each season was then used to estimate an overall average intake of Se in µg/week.

Anthropometric data were not available for participants. Therefore, estimation of Se intake dose standardized for weight used average sex- and age-specific body weights from Canadian Arctic populations [247]. Weekly intake dose of Se was calculated by dividing the overall average intake by estimated body weight (bw), yielding an estimated dose in units of µg/kg bw/week. Given that individuals may consume a much greater amount of fish in one meal than recommended by the Canadian Food Guide, this analysis was also repeated using meal sizes of 100g and 150g, to assess the extent to which assumptions about portion sizes impacted estimates of the effect of Se intake on Hg toxicity (table 32).

To control for the influence of Se on MeHg effects, authoritative experts contend that the intake of Se itself matters less than the molar ratio of Se to MeHg intake [200,202,203], due to the formation of MeHg-Se complexes in fish and marine mammal tissues, which eliminate the bioavailability of MeHg [200–203]. Therefore, EVW converted estimates of the mean concentrations (µg/g) of Hg and Se in the fish and marine mammal species that participants reported consuming to nmol/g (table 31), and then used the formula proposed by Ganther (1972) to estimate the molar ratio of Se to MeHg intake based on nmol/kg bw/day [203]. Using this formula, estimated ratios >1 indicate reduced risk of MeHg toxicity and increased health benefits due to excess Se molecules [203]. EVW also generated the Se Health Benefit Value (HBV) based on nmol/kg bw/day intake of Se and MeHg, estimated using the following formula proposed by Kaneko and Ralston (2007) [202]:

$$HBV = [Se*(Se/MeHg)] - [MeHg*(MeHg/Se)]$$

Using this formula, estimates >0 indicate increased health benefits [202]. Because the unit for consumption frequencies in this study was weeks, these calculations were based on estimated intake in nmol/kg bw/week.

Assessment of Consistency in Diet Over Time

The validity of the approach used to ascertain exposure status rests on the assumption that diet remains reasonably consistent over time. For this reason, EVW repeated the collection of intake frequencies of selected food items ascertained at baseline, to assess the consistency in dietary intake between data collection periods. Food items were selected based on their hypothesized relevance to gastric health outcomes and potential influence on the toxicokinetics of MeHg [63,69,248,249]. The selected food items were: fruit; vegetables (raw and cooked); milk (fresh, packaged or canned); yogurt; pop (regular and diet); coffee; and tea. Average weekly consumption frequencies across all seasons were compared between time points. Participants were also asked whether they take dietary supplements on a regular basis and if so, to specify type and frequency.

Pearson's correlation coefficients were used to estimate the magnitude of the association between diet data collected when FFQs were first administered (2008 in Aklavik, NT; 2010 in Old Crow, YT; and 2012 in Fort McPherson, NT) and during the Hg exposure project in the fall of 2016 [28]. Each food frequency variable was scaled as continuous, representing the reported average number of servings per week. Correlations were estimated for the total study population, as well as by community, gastritis severity, atrophy status, and intestinal metaplasia status.

Findings from published reproducibility studies of dietary intake over extended time periods guided the interpretation of the estimated correlation coefficients. Findings from these studies suggest that correlation coefficients for repeated measurements of intake of specific nutrients over periods spanning 1 to 10 years typically range from 0.5-0.7 [28], while greater variation, with coefficients ranging from 0.34 to 0.7, has been reported for repeated measurements of whole food items over long time periods[28]. While these correlations are of considerably lower magnitude than those obtained through experimental studies in laboratory settings, they are comparable with measurements of other biological indicators in observational studies, where measurements are still found to predict health outcomes with reasonable accuracy [28].

Table 31: *Estimated concentrations of selenium and total mercury in the fish and marine mammal species consumed by participants in studies reported in the literature* [241–245]

Author (Date)	n	Selenium		Mercury		Molar Ratios	
		Mean µg/g	Mean ✣ nmol/g	Mean µg/g	Mean ⌘ nmol/g	Sample Specific	Weighted Average
Burbot (*L. lota*)							
Evans *et al.* (2005)	14	0.19	2.41	0.13	0.65	3.71	
	14	0.75	9.50	0.06	0.30	31.76	
Reyes *et al.* (2016)	6	0.14	1.79	0.32	1.58	1.13	14.80
Arctic Char (*S. aplinus*)							
Evans *et al.* (2005)	5	0.17	2.15	1.30	6.48	0.33	
	5	0.66	8.36	0.21	1.05	7.98	
	4	0.73	9.25	0.55	2.74	3.37	
	14	0.37	4.69	0.20	1.00	4.70	
	18	0.68	8.61	0.16	0.80	10.80	
	10	0.71	8.99	0.14	0.70	12.88	
	8	0.67	8.49	0.29	1.45	5.87	7.67
Beluga Whale (*D. Leucas*)							
Lemire *et al.* (2015)	16	4.35	55.09	0.46	2.29	24.02	
	16	3.52	44.58	0.38	1.89	23.53	
	17	0.73	9.25	1.07	5.33	1.73	
	9	1.26	15.96	4.01	19.99	0.80	
	15	6.25	79.15	10.14	50.55	1.57	11.25
Inconnu (*S. nelma*)							
Evans *et al.* (2005)	3	0.31	3.93	0.19	0.95	4.14	
	3	0.88	11.14	0.17	0.85	13.15	8.65
Arctic Cisco (*C. autumnalis*)							
Evans *et al.* (2005)	10	0.29	3.67	0.03	0.15	24.56	
Reyes *et al.* (2016)	10	0.17	2.20	0.057	0.28	7.75	16.16
Lake Whitefish (*C. clupeaformis*)							
Reyes *et al.* (2016)	15	0.17	2.19	0.07	0.36	6.02	6.02
Broad Whitefish (*C. nasus*)							
Evans *et al.* (2005)	ND *	0.17	2.15	0.05	0.25	8.64	
		0.79	10.01	0.08	0.40	25.09	
		0.08	1.01	0.04	0.20	5.08	
		0.16	2.03	0.25	1.25	1.63	
		0.1	1.27	0.08	0.40	3.18	
		0.11	1.39	0.1	0.50	2.79	
		0.37	4.69	0.17	0.85	5.53	
		0.22	2.79	0.13	0.65	4.30	
		0.23	2.91	0.08	0.40	7.30	
		0.38	4.81	0.09	0.45	10.73	
		0.16	2.03	0.16	0.80	2.54	
		0.35	4.43	0.35	1.74	2.54	
		0.11	1.39	0.15	0.75	1.86	
		0.15	1.90	0.15	0.75	2.54	
		0.25	3.17	0.07	0.35	9.07	
		0.06	0.76	0.08	0.40	1.91	
		0.07	0.89	0.11	0.55	1.62	5.67
Sockeye Salmon (*O. nerka*)							
Kelly *et al.* (2008)	11	0.14	1.77	0.05	0.26	6.84	
Burger *et al.* (2012)	15	0.25	3.17	0.04	0.20	15.88	12.05
Chinook Salmon (*O. tshawytscha*)							
Kelly *et al.* (2008)	10	0.17	2.15	0.09	0.44	4.85	
	11	0.16	2.03	0.07	0.36	5.65	5.27
Chum Salmon (*O. keta*)							
Kelly *et al.* (2008)	12	0.27	3.42	0.02	0.10	34.30	34.30
Pink Salmon (*O. gorbuscha*)							
Kelly *et al.* (2008)	10	0.17	2.15	0.013	0.06	33.22	33.22
Coho Salmon (*O. kisutch*)							
Kelly *et al.* (2008)	10	0.16	2.03	0.04	0.20	10.16	
	12	0.13	1.65	0.05	0.26	6.23	
	13	0.17	2.15	0.06	0.28	7.71	7.90
Dolly Varden (*S. malma*)							
Burger *et al.* (2012)	75	0.35	4.43	0.11	0.55	8.08	8.08

✣ Converted using a molecular weight of 78.96;
⌘ Converted using a molecular weight of 200.59;
* ND = No data – The combined mean values are not weighted

Table 32: *Estimated concentrations of selenium and total mercury in fish and marine mammals by serving size* [241–245]

Fish or Marine Mammal Species §	µg/g	Serving Size		
		µg/ 75g Serving	µg/ 100g Serving	µg/ 150g Serving
Estimated Amount of Selenium				
Coho Salmon (*O. kisutch*)	0.153	11.5	15.3	23.0
Chinook Salmon (*O. tshawytscha*)	0.165	12.4	16.5	24.7
Pink Salmon (*O. gorbuscha*)	0.170	12.8	17.0	25.5
Lake Whitefish (*C. clupeaformis*)	0.173	13.0	17.3	26.0
Sockeye Salmon (*O. nerka*)	0.203	15.3	20.4	30.5
Broad Whitefish (*C. nasus*)	0.221	16.6	22.1	33.2
Burbot (*L. lota*)	0.223	16.7	22.3	33.5
Arctic Cisco (*C. autumnalis*)	0.232	17.4	23.2	34.8
Chum Salmon (*O. keta*)	0.270	20.3	27.0	40.5
Dolly Varden (*S. malma*)	0.350	26.3	35.0	52.5
Arctic Char (*S. aplinus*)	0.577	43.3	57.7	86.6
Inconnu (*S. nelma*)	0.595	44.6	59.5	89.3
Beluga Whale (*D. Leucas*)	0.994	74.5	99.4	149.1
Estimated Amount of Total Mercury				
Pink Salmon (*O. gorbuscha*)	0.013	1.0	1.3	2.0
Chum Salmon (*O. keta*)	0.020	1.5	2.0	3.0
Sockeye Salmon (*O. nerka*)	0.045	3.4	4.5	6.8
Coho Salmon (*O. kisutch*)	0.050	3.8	5.0	7.6
Arctic Cisco (*C. autumnalis*)	0.050	3.8	5.0	7.6
Lake Whitefish (*C. clupeaformis*)	0.073	5.5	7.3	11.0
Chinook Salmon (*O. tshawytscha*)	0.080	6.0	8.0	12.0
Dolly Varden (*S. malma*)	0.110	8.3	11.0	16.5
Broad Whitefish (*C. nasus*)	0.126	9.4	12.6	18.9
Inconnu (*S. nelma*)	0.180	13.5	18.0	27
Burbot (*L. lota*)	0.277	20.8	27.7	41.5
Arctic Char (*S. aplinus*)	0.299	22.4	29.9	44.9
Beluga Whale (*D. Leucas*)	1.649	123.8	165.0	247.5

§ Species ordered according to the concentration of each compound (lowest to highest)

Results

Of the 101 participants who provided hair samples for measurement of MeHg concentration, 64 had gastric pathology outcomes; 16 additional participants who had pathology data provided 2016 data on diet and hair characteristics, but did not provide a hair sample for measurement of MeHg concentration. In total, 80 participants had measured or predicted MeHg concentration in hair and gastric pathology data.

Participant Characteristics

Table 33 shows the distributions of participant characteristics. The 2016 mean age was 53.2 years (SD: 14.7; Range: 20-85 years). The mean age at the time biopsies were collected was 45.9 years (SD: 15.9; Range: 11-82 years). Females were over-represented (64%; 51/80). Participants were predominately residents of Aklavik, NT (64%; 51/80), home of the community *H. pylori* project with the largest number of participants. The prevalence of *H.*

pylori infection was 93% (74/80). The prevalence of each gastric pathology outcome was: 38% (30/80) for severe gastritis; 29% (23/80) for gastric atrophy; and 18% (14/80) for intestinal metaplasia. The severity distributions for all pathology outcomes are shown in table 30.

Table 33: *Socio-demographic characteristics of the subset of participants included in this analysis, all participants who underwent upper endoscopy with gastric biopsy and all participants of the Aklavik, Old Crow, and Fort McPherson community projects (2008-2016)*

Socio-Demographic Characteristics	Total Sample Included in this Analysis (n=80)		All Participants who Underwent Endoscopy (n=289) ⌘		All Participants of Community Projects (n=675) §	
	n	%	n	%	n	%
Community						
Aklavik, NT	51	64	191	66	329	49
Fort McPherson, NT	13	16	52	18	211	31
Old Crow, YT	16	20	46	16	135	20
Age						
Less than 30 years	7	9	73	25	234	35
30-39 years	7	9	41	14	88	13
40-49 years	15	19	58	20	113	17
50-59 years	24	30	62	21	117	17
60-69 years	16	20	34	12	73	11
70 + years	11	14	21	7	50	4
Sex						
Male	29	36	130	45	305	45
Female	51	64	159	55	370	55
Ethnicity						
Non-Indigenous	3	4	22	8	64	9
Inuvialuit	33	41	116	40	194	29
Gwich'in	38	48	136	47	379	56
Other Indigenous	6	8	15	5	38	6
Education Level Completed						
Less than High School	43	54	179	62	429	64
High School ✣	37	46	110	38	246	36

⌘ Participants who underwent endoscopy and had complete data on socio-demographic characteristics
§ All participants of the Aklavik, Fort McPherson and Old Crow *H. pylori* Projects with complete data on socio-demographic characteristics
✣☐Completion of high school corresponds to completion of grade 12

MeHg Concentration

Among the 64 participants with pathology data and hair samples, the mean MeHg concentration was 0.565 µg/g (SD: 0.440; Range: 0.063-2.07 µg/g). Among the 16 individuals with data on diet and hair attributes, the predicted mean MeHg concentration was 0.695 µg/g (SD: 0.226; Range: 0.371-1.08 µg/g). The combined mean MeHg

concentration was 0.591 µg/g (SD: 0.409; Range: 0.063-2.07 µg/g). Table 34 shows the mean percent change in MeHg concentration µg/g for duplicate measurements by outcome status. T-tests comparing the mean values across outcome categories indicated that the variability of duplicate sample measurements was random with respect to outcome status.

Table 34: *Mean percent change in methylmercury concentration (ug/g) values across repeated measurements by outcome status among 23 participants with methylmercury measurements on divided * hair samples and data on gastric health outcomes, 2016*

		% Change in Repeated Measurements of MeHg		
Outcome Status	**n**	**Mean**	**SD**	**p-value**
Chronic Gastritis				
None/Mild/Moderate	15	16.54	11.25	
Severe	8	17.27	9.35	0.88
Gastric Atrophy				
Absent	18	17.08	11.53	
Present	5	15.77	5.43	0.81
Intestinal Metaplasia				
Absent	17	16.48	11.14	
Present	6	17.68	8.88	0.82

**10 participants had samples divided in two by investigators and submitted to lab as unique individuals; 22 participants had samples divided in two by lab personnel, including 4 samples that were duplicates; 4 participants had 3 measurements and their percent change was based on the highest and lowest of the 3 values*

Estimated Intake of Selenium and Mercury

Estimated mean intakes of Se and Hg among participants for different serving sizes are shown in table 35. Among 55 participants who reported regularly consuming fish, the mean molar ratio of Se to MeHg estimated using the Ganther (1972) formula was 7.21 (SD: 7.44; range: 1.53-41.86) [203]. All participants who regularly consumed fish had ratios greater than 1, representing an excess of Se intake relative to Hg intake. Using the Kaneko and Ralston (2007) formula, the mean HBVs among the 55 individuals who regularly consumed fish were: 310.68 (SD: 426.17; range: 12.90-2724.66) for a 75g serving; 414.24 (SD: 568.23; range: 17.20-3632.88) for a 100g serving; and 621.36 (SD: 852.35; range: 25.79-5449.32) for a 150g serving [202]. These estimates are consistent with the calculated ratios, indicating an excess of Se intake relative to Hg intake for all participants who regularly consumed fish.

Table 35: *Estimated mean weekly intake of selenium and total mercury for different serving sizes* [202,203,241–245]

	µg/kg bw/week		nmol/kg bw/week	
Serving Size	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**
Estimated Selenium Intake from Fish and Marine Mammals				
75 g	0.73 ± 1.01	0 - 6.13	37.19 ± 50.92	0 - 310.6
100 g	0.97 ± 1.34	0 - 8.18	49.58 ± 67.89	0 - 414.1
150 g	1.47 ± 2.01	0 - 12.26	74.38 ± 101.8	0 - 621.2
Estimated Mercury Intake from Fish and Marine Mammals				
75 g	0.51 ± 0.83	0 - 5.09	10.92 ± 18.77	0 - 101.5
100 g	0.67 ± 1.10	0 - 6.79	14.57 ± 25.00	0 - 135.4
150 g	1.01 ± 1.65	0 - 10.19	21.85 ± 37.49	0 - 203.0

Association between Hair MeHg Concentration & Gastric Pathology Outcomes

Severe Chronic Gastritis

Table 36 shows the distribution of severe chronic gastritis prevalence across participant characteristics. Purposeful selection of covariates resulted in a multivariable logistic regression model that included: sex; fish consumption in the summer; estimated selenium intake; and hair MeHg concentration. The addition of either a random or fixed effect to account for clustering in communities did not improve the fit of the model or alter effect estimates for other covariates. Table 37 shows unadjusted and adjusted ORs and 95% CIs for the effects on severe chronic gastritis of each hair MeHg concentration level ≥0.25 µg/g compared to <0.25 µg/g. Unadjusted estimates for hair MeHg concentrations between 0.5 and 0.99 µg/g or ≥1 µg/g showed reduced odds relative to <0.25 µg/g; this reduction persisted following adjustment for sex, fish and marine mammal consumption and estimated Se intake.

Model building procedures did not yield evidence of a statistical interaction between selenium intake and hair MeHg concentration, possibly due to insufficient statistical power to detect this relationship [86]. Despite insufficient data for precise estimation of effect-measure modification, a product term for estimated Se intake and hair MeHg concentration was added to the model. Table 38 shows the log odds of severe chronic gastritis for each hair

MeHg concentration level at specified values of Se intake adjusted for sex and total fish consumption. As depicted graphically in figure 17, when Se intake is 0, hair MeHg concentrations ≥1 µg/g are associated with higher log odds of severe chronic gastritis relative to hair MeHg concentrations <1 µg/g, and the log odds decline sharply as Se intake increases.

Table 36: *Prevalence of each of the gastric pathology outcomes stratified by participant characteristics included in the multivariable logistic regression models among 80 participants from 3 western Canadian arctic communities, 2016*

		Prevalence of Gastric Pathology Outcomes		
Participant Characteristics	**n**	**Severe Chronic Gastritis (n=30)**	**Gastric Atrophy (n=23)**	**Intestinal Metaplasia (n=14)**
Sex				
Male	29	57	57	50
Female	51	43	43	50
Age				
Less than 30 years	7	14	14	14
30-39 years	7	57	29	0
40-49 years	15	40	13	13
50-59 years	24	38	21	13
60-69 years	16	44	50	19
70 + years	11	27	45	45
Total Fish Consumption in the Summer				
<1 meals/week	29	45	21	17
1-2 meals/week	13	31	38	15
3-4 meals/week	14	43	36	0
≥ 5 meals/week	24	29	29	29
MeHg in Hair				
<0.25 µg/g	27	30	22	14
0.25-0.49 µg/g	31	37	35	29
0.5-0.99 µg/g	39	23	22	36
≥1 µg/g	20	10	22	21
Selenium Intake from Fish				
<0.5 µg/kg bw */week	44	48	32	16
0.5-0.99 µg/kg bw/week	15	40	27	13
1-2 µg/kg bw/week	20	15	20	20
3-4 µg/kg bw/week	0	0	0	0
≥ 5 µg/kg bw/week	1	0	100	100

* bw = body weight

Gastric Atrophy

Table 36 shows the prevalence of gastric atrophy within categories of selected variables. Model building procedures selected the following variables: sex; age; fish consumption in the summer; estimated selenium intake; and hair MeHg concentration. The estimates from

this model are similar to those from the model of effects on severe chronic gastritis. Specifically, the adjusted ORs for the effect on gastric atrophy of each MeHg concentration level ≥0.50 μg/g show reduced odds relative to concentrations <0.25 μg/g, adjusting for sex, age, total fish consumption and Se intake (Table 37). Table 38 and Figure 17 show the log odds of gastric atrophy for each hair MeHg concentration level at specified values of Se intake adjusted for sex, age and total fish consumption; the adjusted log odds of gastric atrophy are higher among individuals with hair MeHg concentrations ≥1 μg/g compared to those in all lower categories, when Se intake is 0 μg/kg bw /week.

Intestinal Metaplasia

Table 36 shows the prevalence of intestinal metaplasia within categories of selected variables. There were not enough participants with intestinal metaplasia and data on MeHg exposure for precise estimation of effects in a multivariable regression model. Unadjusted ORs for the association of intestinal metaplasia with the covariates included in other models (Table 37) are similar to estimates from models of effects on severe chronic gastritis and gastric atrophy. Conversely, increasing MeHg concentration and Se intake are associated with increased log odds of intestinal metaplasia, although data were insufficient for accurate estimation of log odds of intestinal metaplasia adjusted for other factors.

Progression to More Advanced Gastric Pathologies

Of 80 participants with data on hair-MeHg concentration and gastric pathology outcomes, 7 had no evidence of chronic gastritis, atrophy or intestinal metaplasia. Among 73 participants with evidence of gastric pathologies, the most advanced lesion was: chronic gastritis (graded as mild, moderate or severe) in 60% (44/73); gastric atrophy in 21% (15/73); and intestinal metaplasia in 19% (14/73). The parallel regression assumption was not violated for any of the covariates in the model (overall p-value=0.43). The adjusted ORs and 95%CIs for the adjusted effects of each covariate on progression to more advanced gastric pathologies are shown in table 39 Findings from this analysis were consistent with those from the logistic regression models fit for each outcome alone. Specifically, this analysis showed a reduction in the odds of progressing to a more advanced gastric pathology with hair-MeHg concentrations ≥0.50 μg/g (vs. <0.25 μg/g), adjusted for age, sex, total fish consumption in the summer and estimated Se intake.

Table 37: *Odds ratios for the effects of participant characteristics on prevalence of gastric pathology outcomes among 80 participants from 3 western Canadian arctic communities, 2016*

	Unadjusted		Adjusted ⌘	
	OR	**95%CI**	**OR**	**95%CI**
Severe Chronic Gastritis				
Sex				
Male	*Reference*		*Reference*	
Female	0.75	0.51, 1.11	0.40	0.18, 0.92
Total Fish Consumption				
Per unit increase (meals/week)	0.83	0.64, 1.08	1.70	1.01, 2.89
Selenium Intake				
Per unit increase (µg/kg bw/week)*	0.46	0.25, 0.84	0.27	0.18, 0.41
MeHg in Hair *(µg /g)*				
<0.25	*Reference*		*Reference*	
0.25-0.49	1.02	0.69, 1.51	1.38	1.32, 1.44
0.50-0.99	0.41	0.40, 0.42	0.41	0.35, 0.49
≥1	0.37	0.06, 2.49	0.38	0.04, 3.40
Gastric Atrophy				
Sex				
Male	*Reference*		*Reference*	
Female	0.53	0.50, 0.56	0.22	0.15, 0.32
Age				
Per one-year increase	1.02	1.01, 1.03	1.04	1.01, 1.08
Total Fish Consumption				
Per unit increase (meals/week)	1.12	0.65, 1.92	1.85	0.58, 5.90
Selenium Intake				
Per unit increase (µg/kg bw/week)	1.29	0.81, 2.04	0.30	0.002, 0.50
MeHg in Hair *(µg /g)*				
<0.25	*Reference*		*Reference*	
0.25-0.49	1.27	0.75, 2.15	1.31	0.65, 2.65
0.50-0.99	0.63	0.20, 2.05	0.34	0.12, 0.94
≥1	1.42	0.20, 9.90	0.69	0.10, 4.73
Intestinal Metaplasia				
Sex				
Male	*Reference*			
Female	0.47	0.12, 1.87		
Age				
Per one-year increase	1.05	1.00, 1.10		
Total Fish Consumption				
Per unit increase (meals/week)	1.10	1.07, 1.12		
Selenium Intake				
Per unit increase (µg/kg bw/week)	1.58	1.27, 1.95		
MeHg in Hair *(µg /g)*				
<0.25	*Reference*			
0.25-0.49	1.73	0.37, 8.16		
0.50-0.99	1.96	0.25, 15.23		
≥1	2.65	0.23, 31.20		

⌘ Adjusted for all model covariates
* bw =Body Weight
Note: Models do not contain a product term for the interaction between MeHg and Se

Table 38: *Log odds of severe chronic gastritis and gastric atrophy for methylmercury levels in hair at specified values of estimated selenium intake, adjusted for sex and total fish consumption frequency among 80 participants from 3 arctic communities, 2016* *

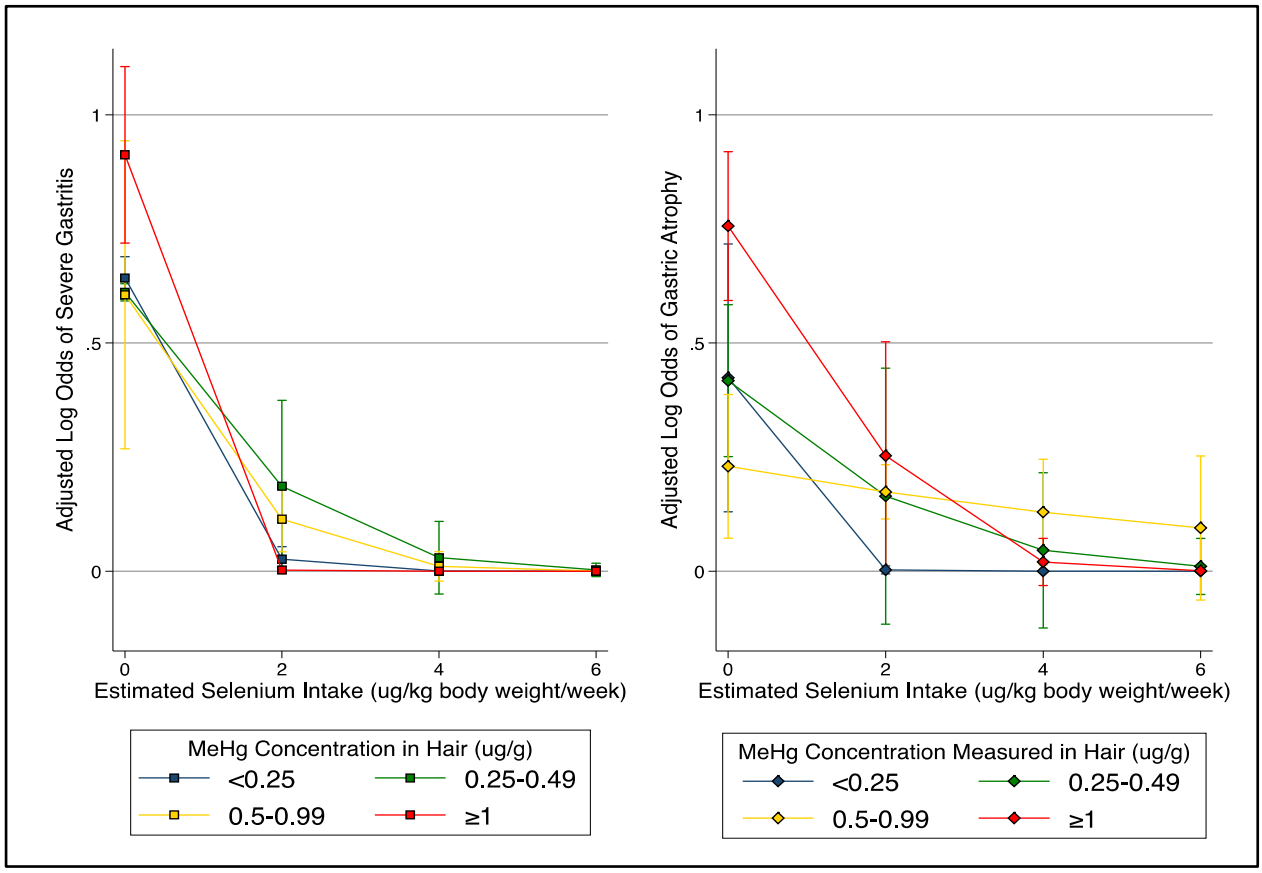
MeHg in Hair	Estimated Se Intake from Fish and Marine Mammals			
	0 (µg/kg bw/week)	2 (µg/kg bw/week)	4 (µg/kg bw/week)	6 (µg/kg bw/week)
Severe Chronic Gastritis				
<0.25 (µg /g)				
Adjusted Log Odds	0.64	0.03	0.0002	$1.74x10^{-6}$
95%CI	0.60, 0.69	-0.001, 0.05	-0.0004, 0.0009	$-6.74x10^{-6}$, 0.00001
0.25-0.49 (µg /g)				
Adjusted Log Odds	0.61	0.19	0.03	0.003
95%CI	0.59, 0.63	-0.002, 0.37	-0.05, 0.11	-0.012, 0.018
0.5-0.99 (µg /g)				
Adjusted Log Odds	0.61	0.11	0.01	0.0002
95%CI	0.27, 0.94	0.04, 0.19	-0.02, 0.04	-0.0009, 0.001
≥1 (µg /g)				
Adjusted Log Odds	0.91	0.003	$9.91x10^{-8}$	$3.87x10^{-12}$
95%CI	0.72, 1.11	-0.005, 0.01	$-6.28x10^{-7}$, $8.26x10^{-7}$	$-4.13x10^{-11}$, $4.91x10^{-11}$
Gastric Atrophy				
<0.25 (µg /g)				
Adjusted Log Odds	0.45	0.002	$2.07x10^{-6}$	$1.77x10^{-9}$
95%CI	0.20, 0.71	-0.009, 0.01	-0.00002, 0.00002	$-2.62x10^{-8}$, $2.98x10^{-8}$
0.25-0.49 (µg /g)				
Adjusted Log Odds	0.41	0.21	0.09	0.03
95%CI	0.28, 0.54	-0.20, 0.63	-0.32, 0.50	-0.21, 0.28
0.5-0.99 (µg /g)				
Adjusted Log Odds	0.13	0.24	0.38	0.55
95%CI	-0.012, 0.28	0.12, 0.35	0.24, 0.52	0.27, 0.83
≥1 (µg /g)				
Adjusted Log Odds	0.73	0.27	0.03	0.0023
95%CI	0.55, 0.90	-0.02, 0.57	- 0.06, 0.12	-0.007, 0.01

* These values are plotted in figure 17

Table 39: *Odds Ratios for the Effects of Participant Characteristics on Progression to more Advanced Gastric Pathologies among 73 Participants from 3 Western Canadian Arctic Communities, 2016*

	Unadjusted		Adjusted	
	OR	95%CI	OR	95%CI
Sex				
Male	*Reference*		*Reference*	
Female	0.52	0.34, 0.79	0.38	0.13, 1.13
Age				
Per one-year increase	1.03	1.00, 1.06	1.04	1.00, 1.08
Total Fish Consumption				
Per unit increase (meals/week)	1.08	0.96, 1.20	1.20	0.91, 1.59
Selenium Intake				
Per unit increase (µg/kg bw/week)*	1.16	0.75, 1.80	0.79	0.25, 1.45
MeHg in Hair *(µg /g)*				
<0.25	*Reference*		*Reference*	
0.25-0.49	1.29	0.45, 3.71	1.27	0.39, 4.21
0.5-0.99	0.68	0.23, 2.02	0.44	0.11, 1.86
≥1	0.84	0.21, 3.37	0.69	0.10, 4.62

Figure 17: *Log odds of severe chronic gastritis and gastric atrophy for methylmercury concentration levels in hair at specified values of estimated selenium intake, adjusted for sex and total fish consumption frequency among 80 participants from 3 arctic communities, 2016*



Consistency in Diet Over Time

Of the 80 participants in this analysis, 75 had complete data on gastric pathology outcomes, baseline diet, and 2016 diet (49 from Aklavik, NT; 14 from Old Crow, YT; and 12 from Fort McPherson, NT). Table 40 shows correlation coefficients comparing baseline and 2016 diet for all participants combined and by community, given that the time period between baseline and 2016 varied by community. These correlations were predominantly within the expected range, based on reproducibility studies of whole food frequencies [28]. The lowest correlation coefficients in the total study population were for milk and yogurt. Estimates of the correlation between repeated measurements of fruit and milk intake were particularly low among participants from Fort McPherson, NT, though the small number of participants from Fort McPherson in this analysis should be noted [28]. Inspection of community-specific

estimates does not reveal a clear pattern relating the magnitude of the correlation coefficients to the length of time between data collection points. Table 41 shows correlation coefficients stratified by gastric pathology outcome status for assessment of how misclassification of diet may depend on outcome status. The largest absolute differences in correlation coefficients were between participants with and without intestinal metaplasia. While useful for bias analysis, this assessment does not yield conclusive inferences about the dependence of diet measurement error on community or outcome status, given the small number of participants in each stratum [28].

Table 40: *Pearson's correlation coefficients comparing measurements obtained during the original data collection period and repeated in fall 2016 by community among 75 participants with complete data*

Food Item	All Participants (n=75)	Community		
		Aklavik (n=49)	Old Crow (n=14)	Ft. McPherson (n=12)
Fruit	0.53	0.63	0.58	0.07
Vegetables	0.49	0.47	0.81	0.58
Milk	0.20	0.40	0.15	0.04
Yogurt	0.25	0.14	0.46	0.52
Pop	0.39	0.34	0.65	0.73
Coffee	0.70	0.71	0.34	0.56
Tea	0.82	0.82	0.86	0.57
Total Fish	0.32	0.35	0.44	0.20

Table 41: *Pearson's correlation coefficients comparing measurements obtained during the original data collection period and repeated in fall 2016 stratified by outcome status, among 75 participants with complete data*

Food Item	Chronic Gastritis Severity		Gastric Atrophy		Intestinal Metaplasia	
	Severe (n=28)	Not Severe (n=47)	Present (n=20)	Absent (n=55)	Present (n=12)	Absent (n=63)
Fruit	0.44	0.57	0.49	0.54	0.91	0.36
Vegetables	0.48	0.52	0.65	0.40	0.87	0.41
Milk	0.21	0.20	0.44	0.12	-0.07	0.28
Yogurt	0.07	0.32	0.62	0.15	0.67	0.17
Pop	0.22	0.41	0.15	0.42	0.79	0.32
Coffee	0.74	0.70	0.68	0.70	0.91	0.57
Tea	0.87	0.78	0.89	0.76	0.33	0.84
Total Fish	0.43	0.25	0.48	0.26	0.37	0.32

Discussion

This investigation of the effect of MeHg exposure through fish and marine mammal consumption on the prevalence of three gastric pathology outcomes highlighted the important interaction between MeHg and Se. The adjusted log odds of severe chronic gastritis and gastric atrophy were highest among individuals with hair MeHg ≥1 µg/g, relative to those with lower MeHg concentrations when estimated Se intake from fish was 0 µg/kg bw/week. As Se intake increased, log odds of both gastric pathology outcomes decreased for participants in all categories of hair MeHg concentration (µg/g). All participants who regularly consumed fish or marine mammals had estimated Se:Hg ratios >1. Additionally, the estimated HBVs for all fish-consuming members of the study population were >0. These findings suggest that most Hg consumed from eating fish and marine mammals was sequestered by Se and rendered toxicologically inert [200,250]. Assuming the values used to estimate these ratios are representative of the true exposure among participants, residual toxic effects could be related to insufficient Se resulting from MeHg exposure [200,250]. Specifically, since MeHg bonds competitively with Se molecules, the supply of Se would be depleted by MeHg, leaving the individuals susceptible to the toxic effects of other compounds that would otherwise be sequestered by Se [200,250].

Adjusted ORs and 95%CIs for the effects of each category of MeHg concentration ≥0.50 µg/g (vs. <0.25 µg/g) on prevalence of each of the gastric pathology outcomes and progression to more advanced lesions wee consistent with protective effects. While there are no reports in the published literature of epidemiological studies investigating MeHg exposure and gastric pathology outcomes, findings of a protective effect of higher hair MeHg concentrations on gastric pathology is inconsistent with the literature on toxicological consequences of MeHg exposure [251–253]. However, decreasing toxicological effects with increasing MeHg exposure have been observed in epidemiological studies investigating other health outcomes associated with exposure [251–253]. A proposed explanation for these contradictory findings is suboptimal statistical modeling of the complex relationship between Se and Hg [200]. Se is an essential nutrient that confers important health benefits, but has a biphasic effect characterized by increasing health benefits up to a threshold of intake, after which it induces toxic effects [28,200,202,203,250]. Authoritative experts have suggested that when Se intake exceeds toxic thresholds, MeHg may confer protection by sequestering excess Se and eliminating its toxic effects [200,250]. Health Canada has defined this threshold at 50 µg/g/day, or 350 µg/g/week [254]. The estimated mean body weights used for this analysis were 76 kg for males and 70 kg for females [247]. Using these values, the estimated Se intake

threshold for this population would be 0.66 µg/g/day (4.61 µg/g/week) for males and 0.71 µg/g/day (5 µg/g/week) for females. Based on estimated intake from fish alone only 1 female participant had estimated intake exceeding these thresholds (75g serving: 6.13 µg/g/week; 100g serving: 8.18 µg/g/week; 150g serving: 12.26 µg/g/week). However, dietary Se intake is not exclusively from fish and marine mammals, so the values estimated for this analysis do not capture total Se intake [28,200].

In general, this study was limited by insufficient data for precise effect estimation, including an interaction between hair MeHg concentration and estimated Se intake. Additionally, this study was limited by the lack of biochemically measured Se levels. The accuracy of Se intake values estimated from FFQ data and published Se concentrations in the species that participants consume rests on the accuracy of the food frequencies reported by participants and the assumption that the Se concentrations in these species remains approximately constant [28]. Se concentrations in food items such as farm-raised meats and vegetables has been shown to fluctuate drastically due to variation in Se concentrations in soil across geographic regions [28]. Thus, approximation of Se intake through such food items is not considered reliable; therefore, this analysis did not use Se intake from foods other than fish and marine mammals [28]. To the extent that Se intake from other food sources is not proportional to Se intake from fish and marine mammals, inability to accurately approximate total Se intake Se may have resulted in residual confounding by Se of the MeHg effects. To the extent that biochemical interactions between Se and MeHg and other mechanisms of effect-measure modification extend beyond their simultaneous intake through fish and marine mammals, the statistical models used in this analysis may not accurately reflect the influence of Se intake on the relationship between MeHg exposure and gastric pathology outcomes. Additionally, this analysis was not able to assess the extent to which participants were consuming Se at levels above the toxicity threshold.

For most food items, correlation coefficients comparing the baseline serving frequencies obtained when the gastric pathology outcomes were ascertained to the 2016 serving frequencies were in the expected range for this type of data [28]. However, given the 4-8-year time interval between the two data collection points, differences in responses likely reflect a combination of measurement error and true changes in diet [28]. It should be noted that correlations between time points could reflect correlated errors in food frequency reporting by participants [28]. This analysis did not have sufficient data for accurate assessment of whether the variations in reported food frequencies over time differed by gastric pathology

outcome status. Future research should include a quantitative bias analysis to assess the extent to which misclassification error influenced inferences drawn from this analysis. To achieve this, regression models should be constructed, using the original variables representing consumption of a given food item as the dependent variables and the repeated measurements as covariates [28]. Regression coefficients, representing the magnitude of the change in the originally measured variable with changing values of the repeated measurement, could then be used to adjust estimates of the effects of consumption of that food item on gastric pathology outcomes [28].

While the variable representing Se intake through fish was an approximation with inherent limitations, the relationship between Se intake and other variables in the model behaved in expected ways, which provides qualitative evidence of the validity of the classification of participants' Se status for the goals of this analysis [28]. For example, model estimates showed strong inverse associations of increasing Se intake with the prevalence odds of both severe chronic gastritis and gastric atrophy, consistent with evidence of health benefits from Se intake [28]. Unadjusted estimates for total fish and marine mammal consumption reflected null effects of increasing intake on the prevalence odds of both severe chronic gastritis and gastric atrophy. When Se intake was included in the models, the association between total fish consumption and each gastric pathology outcome reflected deleterious effects, consistent with evidence highlighting the potential for a wide variety of contaminants that accumulate in fish tissue to contribute to the pathogenesis of gastric pathology [255]. While adjustment for Se intake did not explain the overall inverse association between hair MeHg concentration and gastric pathology outcomes, estimates of the adjusted log odds of both severe chronic gastritis and gastric atrophy among those with no Se intake from fish were higher among those with higher MeHg concentrations.

Conclusions

This research provides evidence of a potential relationship between higher MeHg exposure and gastric pathology outcomes, which is modified and mediated by Se intake. These analyses were limited by insufficient data for precise estimations of effects of interest and lack of biochemical measurements of Se intake. However, to our knowledge, this is the first population-based epidemiological analysis investigating the effects of MeHg exposure on gastric health outcomes. Therefore, within the methodological constraints of this research, findings contribute to a comprehensive understanding of diverse health outcomes related to MeHg exposure.

Chapter 5: Conclusions

Summary of Findings

Paper 1: Fish Consumption and Human Tissue Concentrations of Mercury: Using Meta-Analysis to Investigate Heterogeneity across Populations Worldwide

This systematic review aimed to identify and summarize the published literature pertaining to human tissue concentrations of mercury (Hg) and consumption of fish or seafood. Articles were included in the review if they presented tissue concentrations of Hg stratified by categories of fish consumption, defined by frequency of meals, amount of fish or the type of fish consumed. A total of 87 articles were selected for inclusion in the review, representing populations from around the globe. Of the included articles, 25 reported Hg concentrations measured in blood, 67 reported Hg concentrations measured in hair, and 4 reported Hg concentrations measured in urine. The most common biomarker was total mercury (THg). Methylmercury (MeHg) was measured in hair in 2 studies, and in blood in 4 studies.

The goals of the meta-analysis were to quantify the extent to which the relationship between fish or seafood consumption frequency and tissue concentrations of Hg remains consistent across populations represented in the published literature and the extent to which characteristics like age and sex account for variation across populations. Two approaches addressed these aims. First, summary data extracted from published reports permitted descriptive analysis and multivariate random-effects meta-regression to estimate the degree of between-study heterogeneity simultaneously for the effects on hair THg concentration of ≥3 vs. 1-2 fish-meals/week and 1-2 vs. <1 fish-meals/week. Second, raw data provided by a subset of authors was pooled and analyzed using multivariable random-effects regression models. In the pooled analysis of raw data, a random intercept and random slope for each level of fish consumption frequency allowed quantification of heterogeneity across studies with respect to baseline levels of mercury in hair and to the magnitude of the change in hair-Hg concentration across subsets of each study population stratified by level of fish consumption.

The analysis of summary data included 13 studies. Results from this analysis showed a high degree of variation across studies, particularly for the effect of consuming ≥3 vs. 1-2 fish-meals/week on hair THg concentration. The magnitude of this variation was not reduced by adjustment for the mean age of the study population, or the proportion that was male or female. Inclusion of a variable representing the geographic location slightly reduced the standard deviation representing the residual variation across studies.

Of the raw datasets provided by authors, 5 had exposure categorizations that differentiated higher consumption frequencies [104–106,108,110]. Analysis of pooled datasets that included different subsets of studies based on how fish consumption was categorized yielded similar conclusions to those of the summary analysis. There was a high degree of between-study variation for all exposure contrasts, with a particularly high level of variation for the effect of consuming ≥4 vs. <1 fish-meals/week on hair THg concentration, after adjusting for age and sex. A sensitivity analysis demonstrated that the magnitude of the standard deviation representing residual variation across studies estimated for this contrast was not due to the open-ended nature of the highest category of fish consumption. Exposure status was categorized with greater differentiation at lower consumption frequencies in 3 of the datasets provided by authors [106–108]. When pooling these 3 datasets, the magnitude of the estimates of residual variation across studies was smaller than that of other analyses, but proportional to the mean hair THg concentration among individuals represented in the data. Overall, findings from this research demonstrate that accurate assessment of exposure to Hg through dietary intake requires consideration of factors beyond age and sex.

Paper 2: Patterns of Fish Consumption and Concentrations of Methylmercury in Hair among Residents of Western Canadian Arctic Communities

This dissertation research component aimed to measure exposure to MeHg among participants of CAN*Help* Working Group projects from Aklavik NT, Fort McPherson NT, and Old Crow, YT. A food frequency questionnaire (FFQ) developed for this research in consultation with community representatives focused on consumption of locally harvested fish and marine mammals. The FFQ ascertained the species of fish or marine mammal consumed, as well as parts of the fish or marine mammal consumed, the usual methods of preparation and the seasons within which each species is most often consumed. Fieldwork took place in the fall of 2016 (September-November). All residents from each community were invited to participate. At the time of the interview, participants also responded to a

second FFQ that measured intake of other food items hypothesized to be related to the toxicokinetics of MeHg and the development of gastric pathologies. Additionally, hair samples for biochemical measurement of MeHg concentration were collected from each participant. Characteristics of the hair were documented, including: length (cm), use of hair dyes or other permanent treatments and time since most recent treatment.

A total of 101 participants (45 from Aklavik, 32 from Old Crow and 24 from Fort McPherson) provided data on diet and hair samples for measurement of MeHg concentration. The mean MeHg concentration in participants from all communities combined was 0.60 µg/g (SD: 0.47; Range: 0.059 – 2.07). None of the participants had hair-MeHg concentrations that exceed exposure maximums defined by Health Canada. Participants reported consuming 17 different species of fish or marine mammals in the past 12 months. The most commonly reported species were Broad Whitefish (*C.nasus*) (83%), followed by Inconnu (*S.nelma*) (42%) and Dolly Varden (*S.malma*) (33%). There was variation across communities and seasons with respect to species consumed. Given seasonal variation in availability of different species and subsequent seasonal variation in consumption frequencies, the analysis used separate variables representing season-specific consumption frequencies.

This research component highlighted the large proportion of participants from Aklavik, Fort McPherson and Old Crow who consume a wide range of fish species. There was a positive association between consumption of fish and marine mammals and hair-MeHg concentration in each season, after adjusting for sex, hair length and use of hair dyes or permanent treatments. However, MeHg concentrations measured in the collected hair samples were low overall, suggesting that the participants' fish and marine mammal consumption habits were not placing them at elevated risk of serious health outcomes known to result from Hg exposure.

Paper 3: Investigating the Effect of Dietary Exposure to Methylmercury on Gastric Health Outcomes

The last dissertation research component aimed to estimate the effect of MeHg exposure on the prevalence of three gastric pathologies: severe chronic gastritis; gastric atrophy; and intestinal metaplasia. Of 101 participants who provided hair samples for biochemical measurement of MeHg concentration, 64 had also provided gastric biopsies for histopathological evaluation. An additional 16 individuals provided gastric biopsies for histopathological evaluation and data on fish and marine mammal consumption habits in

2016, but did not provide hair samples for biochemical measurement of MeHg concentration. For this subset of the population, hair-MeHg concentrations were imputed using predicted values from a statistical model built with data on fish consumption during the summer from 101 individuals with hair-MeHg concentrations and FFQ data from 2016. A total of 80 individuals were included in models that estimated the effect of internal MeHg dose measured in hair on the prevalence of each of the gastric pathologies. Findings from this component yielded evidence of a relationship between higher concentrations of MeHg measured in hair and increased odds of severe chronic inflammation and gastric atrophy, which may be mediated and modified by selenium intake.

Summary of Limitations

Paper 1: Fish Consumption and Human Tissue Concentrations of Mercury: Using Meta-Analysis to Investigate Heterogeneity across Populations Worldwide

The analysis of summary data were limited by the small number of studies available for inclusion. Because characteristics were measured at the study level, this restricted the ability to adjust estimates of between-study heterogeneity for multiple characteristics at a time, since stratification on multiple factors left very few studies within each stratum. In models with multiple covariates, sparse data could impact the performance of the multivariate random-effects meta-regression method. The pooled analyses were limited by lack of available data on factors hypothesized to influence Hg toxicokinetics, which limited the ability to estimate the influence of these factors on between-study heterogeneity in the relationship between fish consumption frequency and hair mercury concentrations. An additional limitation was that each study measured THg, but most reports did not contain information on sources of exposure to Hg other than fish. If the degree of exposure to Hg through other sources was not proportional across categories fish and marine mammal consumption frequencies, this could explain some of the residual variation in the effect of fish consumption on hair THg estimated across studies.

Paper 2: Patterns of Fish Consumption and Concentrations of Methylmercury in Hair among Residents of Western Canadian Arctic Communities

The high degree of variation in hair length among the collected samples (median: 1.1 years; IQR: 2.1 years) could have impacted the comparability across samples obtained from participants whose hair had been growing for different periods of time. Inclusion of hair length as a covariate in multivariable regression models may not have adequately accounted for the differential relationship between hair as a reflection of exposure during a defined calendar period and consumption of fish or marine mammals in each season. These analyses were also limited by insufficient data for precise estimation of some effects of interest on hair-MeHg levels. In particular, this research would have benefited from investigation of the relative impact of each individual species of fish and marine mammal that participants reported consuming. Additionally, more data would have allowed a more comprehensive assessment of the potential for other dietary factors to modify the effect of fish or marine mammal intake on hair-MeHg concentrations.

Paper 3: Investigating the Effect of Dietary Exposure to Methylmercury on Gastric Health Outcomes

This dissertation research component was limited by insufficient data for precise estimation of effects of interest, including interaction between hair MeHg concentration and estimated selenium (Se) intake. These analyses were also limited by the inability to measure biochemically the internal dose of Se for each participant. The accuracy of Se intake estimated from food frequency data provided by participants rests on the following assumptions: the reported intake frequencies for each type of fish and marine mammal were accurate; and the Se content of each species that participants reported consuming remains reasonably constant [28]. To the extent that the assumptions made in estimating Se intake from fish and marine mammals were violated, or intake of Se from other food sources was not proportional to Se intake from fish or marine mammals, inaccurate approximations of Se intake may have resulted in residual confounding by Se of MeHg effects. To the extent that biochemical interactions between Se and MeHg extend beyond their simultaneous intake through fish and marine mammals, the statistical models used in this analysis may not accurately account for the influence of Se intake on the relationship between methylmercury exposure and gastric pathology outcomes. Finally, the analysis was unable to estimate whether average intake of Se among participants surpassed the toxicity threshold.

Summary of Strengths

Paper 1: Fish Consumption and Human Tissue Concentrations of Mercury: Using Meta-Analysis to Investigate Heterogeneity across Populations Worldwide

A major strength of this component was the use of optimal approaches for systematic reviews and meta-analyses, as described by authoritative resources in the field [86,88]. The review followed strict *a priori* inclusion and exclusion criteria for article selection to ensure that the search results were reproducible and the assessment of each article's eligibility for inclusion was systematic. In particular, multiple reviewers independently assessed the eligibility of abstracts and articles identified in database searches and extracted data from the selected articles. The two approaches to the meta-analysis conferred distinct advantages. Analysis of summary data presented in published articles led to the inclusion of a larger number of studies and therefore a more diverse set of populations were represented in the analysis. Analysis of pooled data is considered the optimal approach to meta-analysis [86]. Since raw datasets were provided by a subset of authors, statistical methods appropriate for use in single studies could be applied to the merged raw data [86]. The pooled analysis had sufficient statistical power for precise estimation of the effect of fish consumption frequency on hair THg concentrations, adjusting for multiple participant characteristics and assessing the presence of effect-measure modification [86].

Paper 2: Patterns of Fish Consumption and Concentrations of Methylmercury in Hair among Residents of Western Canadian Arctic Communities

A major strength of this research component is the close partnership and collaboration with members of participating Indigenous communities. Since this research aimed to address concerns raised by community members, there was a high level of community engagement in developing data collection methods and participating in this research component. Before the data collection instruments were developed, local representatives provided information on key aspects of fish and marine mammal harvesting and consumption practices among community members. This information improved the accuracy of the collected data, by informing the development of the fish-focused food frequency questionnaire and timing of hair sample collection. In particular, input from local representatives led to the incorporation of commonly used names for different species, which likely improved participants' ability to provide accurate responses.

Paper 3: Investigating the Effect of Dietary Exposure to Methylmercury on Gastric Health Outcomes

This component of the research also benefited from the strong collaborative relationship with the participating communities. The use of biochemical measurements of MeHg concentration in hair samples to ascertain exposure levels is another important strength of this research. Biomonitoring is considered the optimal approach for measuring exposure status in studies that aim to investigate associated health effects [82,85]. This is because biomonitoring directly measures the internal dose of chemicals of interest and accounts for inter-individual variation in rates of metabolism and excretion [82,85]. Further, the systematic approach to collection and analysis of gastric biopsies improved the validity of outcome ascertainment. In each community, an endoscopy unit was set up in the local health center, using equipment provided by Olympus Canada and staffed by a team of gastroenterologists and specialized nurses from the University of Alberta. Sending a team of specialists to the community conferred two important benefits. First, having gastroenterologists obtain the biopsies improved the overall quality of the biopsies. Second, since these communities are located in remote regions, those seeking care from specialists typically have to travel to major urban centers. Therefore, this provided a valuable opportunity for a large proportion of each community to be seen by specialists about their gastrointestinal health concerns. Finally, a single pathologist who specializes in gastric pathologies evaluated the biopsies.

Summary of Scientific Contributions

Paper 1: Fish Consumption and Human Tissue Concentrations of Mercury: Using Meta-Analysis to Investigate Heterogeneity Across Populations Worldwide

According to a thorough review of the literature, this is the first systematic review that summarizes the published literature presenting biomarker concentrations of Hg stratified by fish consumption frequencies in populations around the globe, without restricting inclusion to specific subsets defined by sex, life stage or occupation. This comprehensive summary of the body of evidence represented in the published literature included a critical evaluation of the evidence, and can be used to guide the development of methods in studies aiming to estimate mercury exposure through diet and to measure internal dose of mercury. Further, to our knowledge, this is the first meta-analysis of data from human populations aiming to:

assess the presence and shape of a dose-response relationship between fish or seafood consumption frequency and hair-THg concentrations and assess heterogeneity across studies that represent subgroups of the global population. The use of advanced statistical methods to meet these aims makes a valuable contribution to the scientific literature on the topic of human exposure to Hg through fish, by investigating the validity of commonly made assumptions about the relationship between fish or seafood consumption and tissue concentrations of Hg. Findings from the meta-analyses can be used to develop new lines of inquiry pertaining to factors that mediate the relationship between estimated intake and tissue concentrations of Hg.

Paper 2: Patterns of Fish Consumption and Concentrations of Methylmercury in Hair among Residents of Western Canadian Arctic Communities

This dissertation research component contributes to the body of evidence pertaining to MeHg exposure among residents of remote Arctic communities. In particular, this MeHg exposure project targeted residents of inland communities, which receive territory-wide advisories about fish consumption and MeHg exposure, but do not receive concurrent assessments of human exposure levels. Although only a small proportion of each community participated in the MeHg exposure project, these findings may aid territorial authorities in developing messages about the likely degree of mercury exposure through fish consumption. Given the nutritional, cultural, social, and economic importance of consuming locally harvested fish to Indigenous Arctic peoples, the observation that participants' hair MeHg concentrations were at levels deemed safe regardless of their fish and marine mammal consumption frequencies, provides useful reassurance to Arctic communities.

Additionally, although the potential for hair dyes and permanent treatments to influence the reliability of measurements in hair has been acknowledged in the scientific community, data on the effect of these treatments on measurements used in epidemiologic analysis is relatively limited. This is because many investigators restrict study populations to individuals who do not use hair dyes or permanent treatments, and thus their studies cannot estimate the direction and magnitude of the effect of these treatments on measurements made in hair. Therefore, findings of lower concentrations of MeHg in hair samples from individuals who used hair dyes or permanent hair treatments relative to those who did not within the same food frequency categories contributes to a limited body of evidence pertaining to factors influencing the reliability of biomarker measurements in hair.

Paper 3: Investigating the Effect of Dietary Exposure to Methylmercury on Gastric Health Outcomes

While MeHg exposure and subsequent health effects has been the focus of a large body of research, epidemiologic investigation of the effect of chronic MeHg exposure on gastrointestinal disease is lacking. Therefore, within the methodological constraints of this component of the research, the findings contribute to a comprehensive understanding of diverse outcomes related to MeHg exposure and point to directions for future research. In particular, evidence that Se in fish and marine mammals may provide some protection against harmful effects of consuming MeHg in fish and marine mammals contributes valuable knowledge about the modern-day health effects of key aspects of the Indigenous Arctic diet in the context of public concern about increasing MeHg concentrations in Arctic wildlife. Though limited in statistical power, this analysis lays the groundwork for a more sophisticated consideration of the effect on human health of MeHg in fish and marine mammal species, taking Se concentrations into account.

Recommendations for Future Research

In studies aiming to estimate the health effects of dietary exposure to chemicals, biomonitoring confers important advantages over other methods of exposure ascertainment [82,85]. Specifically, tissue concentrations can provide a measurement of the internal dose, accounting for inter-individual differences in metabolism and rates of excretion [82,85]. For this reason, biochemical measurement of chemical concentrations in human tissues should be incorporated in these studies when possible. It is crucial that the methods chosen for measuring dietary intake correspond with the exposure window represented in the tissue chosen for biochemical measurement of internal dose. Additionally, it is crucial to consider the inherent limitations on inferences drawn from studies that use each tissue type for validly interpreting the findings.

Future research should investigate factors that mediate the relationship between intake of Hg through fish or seafood and measured tissue concentrations. Such evidence would greatly advance several aspects of this field of research. In particular, it would improve the validity of exposure assessment methods relying on food frequency data and estimated concentrations of Hg in foodstuffs, which are commonly used in regulatory settings and in

studies that lack the resources required for laboratory analysis of tissue samples. Additionally, it would provide greater insight into the causal pathways between intake of fish or seafood contaminated with Hg and various associated health outcomes. Being able to better distinguish factors that mediate the relationship between intake and internal dose from those that mediate the relationship between internal dose and toxic effects would likely yield new strategies for intervening in either mechanism. Finally, this body of evidence could provide insight into subgroups of the population that may be more susceptible to higher body-burdens of Hg following exposure and subsequent negative health effects. This information could be used to target public health strategies for reducing those risks.

In studies aiming to measure internal dose of Hg, biochemical measurement of Hg exposure in human tissues should be accompanied by concurrent measurements of Se exposure. The choice of tissue for measurements of Se concentration should be selected on the basis of the toxicokinetic properties of Se and also should correspond to a similar time window to exposures captured in the tissue selected for Hg measurements. Internal dose of Hg, and in particular MeHg, should be measured in hair. Investigators using hair to measure chemical concentrations should consider including individuals with chemically treated hair to build a larger body of evidence on the influence these treatments have on the reliability of measurements so as to avoid selection bias in epidemiologic studies that rely on measuring biomarkers in hair, given that hair treatments are common in adult populations.

This research yielded evidence consistent with a relationship between exposure to low levels of MeHg and the severity of gastric pathology outcomes. However, the methodological constraints of this research limited the statistical precision of the estimated trends and the ability to adequately adjust for confounders. Therefore, larger epidemiologic studies are needed to gain a better understanding of the role of MeHg in the pathogenesis of gastric disease. Such evidence is crucial in a time of environmental degradation on a global scale.

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Appendices

Appendix 1: Information Sheet

[Insert community name] *H. pylori* Project Information Sheet: Mercury Exposure and Stomach Health

Principal Investigator: Karen Goodman, PhD, Epidemiology, University of Alberta
Project Lead: Emily Walker, MSc, Epidemiology, University of Alberta

About Mercury

Mercury is a chemical element that exists in the environment naturally as well as from human activities. This chemical presents a major environmental health threat, as it is able to induce serious health problems among people who are exposed to high levels.

Mercury is able to accumulate in fish and marine mammals. Eating fish, fish products and marine mammals is considered the most common source of mercury exposure for humans. The concentration of mercury in fish or marine mammals varies across species, ranging from very low to very high. For this reason, the level of exposure to mercury varies by the types of fish and marine mammals that a person eats.

Exposure to high levels of mercury has been associated with nervous system impairments and kidney disease. A growing body of research has also shown an association between exposure to high amounts of mercury and heart and blood vessel diseases. However, effects on other organ systems are poorly understood in the scientific community. And little is known about the health effects of low levels of exposure.

Study Purpose

The CAN*Help* Working Group projects, including the [insert community name] *H. pylori* Project, have shown that severe inflammation of the stomach is more common than expected among participants with *H. pylori* infection in these projects. Project Lead Emily Walker became interested in designing research to learn more about why the frequency of severe inflammation of the stomach is so high in these northern communities. She visited communities participating in CAN*Help* Working Group projects to ask people about their concerns, so that her research can address them. Most people she spoke with mentioned that they worried about mercury being in their traditional foods due to environmental contamination.

The purpose of this study is to investigate the extent to which exposure to mercury in food is associated with the severity of stomach inflammation among people with *H. pylori* infection.

Study Procedures

We will start by assessing exposure to mercury among participants, so we can see later the extent to which it is associated with the severity of stomach inflammation.

Since one of the most common ways people get exposed to mercury is through eating fish, and some types of fish have higher mercury levels than others, we need to learn more about what types of fish participants eat and how often.

To see how people's fish-eating habits relate to how much mercury is in their body, we would like to take small samples of hair from participants and use it to measure mercury levels. Hair samples will be taken from the back of the head. A small bundle of hair will be cut with scissors close to the scalp. Only a small amount of hair will be taken, 120 mgs or about 100 hairs. The missing hair will not be noticeable.

Possible Benefits

We will present study findings to northern health officials so they can decide how to manage any health issues that are potentially related to mercury exposure. If you agree, we will give the results from the hair mercury test to the local health centre nurse for use in monitoring your health.

Your participation will help researchers learn more about the extent to which residents of northern communities are exposed to mercury through fish consumption. This will help health authorities know how serious this problem is so they can develop solutions for reducing health risks. Results from this project will also give us more information about whether mercury exposure is associated with stomach health in your community.

Possible Risks

We will respect your privacy, but may ask some questions you do not wish to answer. If we ask any questions that make you uncomfortable, you can tell us you prefer not to answer. There is no known risk from taking the hair sample.

Confidentiality

During the study we will collect information about you for research purposes. We will do everything we can to make sure that this information is kept private. No data relating to this study that identifies you will be released outside of the research project office or published by the researchers. Sometimes, we may be required by law to release your information with your name, so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure your information is kept private. If you give us permission, the project staff will collect information from your personal health records held at the local health centre. The personal information we get from your records will be only what we need for the research. It is important that we get accurate information for research. For this reason the information we get from you, including your name, may be reviewed by research project staff and members of the University of Alberta Research Ethics Board.

By signing this consent form you are giving permission for the research project staff to collect, use and disclose information about you as described above. After the research is done, we are required to securely store information collected from you for the research. At the University of Alberta, we are required to store research data for 5 years after the end of the study. If you stop participating in the study, we will not collect new information about you, but we will need to keep the information that we collect while you participate in the research.

Voluntary Participation

Your participation in this study is strictly your choice. If you do not wish to participate, it will not affect the care you receive at your local Health Centre. If you enrol in the study, you can stop participating at any time, and it will not affect the care you receive at your local Health Centre.

Expenses

You will not have to pay for any tests or treatment done as part of this study. We do not pay you for your participation. Your participation is voluntary.

Contact Names and Telephone Numbers

If you have concerns about your rights as a study participant, you may contact the University of Alberta Health Research Ethics Board at 780-492-2615. This office is independent of the study investigators.

Please contact any of the individuals identified below if you have any questions or concerns about the research now or later:

Emily Walker, MSc, Project Lead, Edmonton, Alberta
Tel. 1-855-492-2525 (Toll-free) ***e-mail*** emily.walker@ualberta.ca

Karen Goodman, PhD, Lead Investigator of the CAN*Help* Working Group
Tel. 780-492-1889 ***e-mail*** kgoodman@ualberta.ca

Appendix 2: Consent Form

UNIVERSITY OF ALBERTA
Division of Gastroenterology, Katz Group Centre, Edmonton, AB, T6G 2E1

CAN Help WORKING GROUP

[Insert Community Name] *H. pylori* Project Consent Form: Mercury Exposure and Stomach Health

Principle Investigator: Karen Goodman, PhD Phone Number: 780-492-1889
Project Lead: Emily Walker, MSc Phone Number: 1-855-492-2525 (Toll-free)

(To be completed by the research participant)

Do you have questions about the project at this time? No, or questions were answered ☐

Are you satisfied by the information you have received about the project at this time? Yes ☐

	YES	NO
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand you can ask more questions later on if you like?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Do you understand that you are free to withdraw from the study at any time, without having to give a reason and without affecting your future health care?	☐	☐
Has the confidentiality of personal information collected for this research been explained to you?	☐	☐
Do you understand who will have access to personal information collected for this research?	☐	☐
Is it okay with you for us to give your tests results to the health center staff to include in your medical record?	☐	☐

Who explained this study to you? _____

I agree to take part in this study: **YES** ☐ **NO** ☐

Signature of Research Participant _____

(Printed Name) _____ Date:_____

Signature of Witness_____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee _____ Date:_____

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH PARTICIPANT

Appendix 3: Questionnaires

Food Frequency Questionnaire: Fish Consumption

Interview Date _____ Interviewer's Name _____

Participant's Name _____ Participant's ID _____

Which of the following types of fish have you eaten in the past 12 months?

☐ Lake Whitefish (Crooked back) ☐ Broad Whitefish ☐ Inconnu (Coney)

☐ Herring (Arctic Cisco) ☐ Big Eye Herring (Least Cisco) ☐ Pickerel (Walleye)

☐ Arctic Char ☐ Arctic Grayling (Bluefish) ☐ Dolly Varden (Bull Trout)

☐ Burbot (Loche) ☐ Coho Salmon ☐ Lake Trout ☐ Northern Pike (Jackfish)

☐ Chinook Salmon ☐ Chum Salmon ☐ Beluga Whale

☐ Other; Please Specify: _____

Lake Whitefish (Crookedback)

When are Lake Whitefish in Season? _____

Where do you usually get Lake Whitefish from? _____

In Season

When in season, do you eat Lake Whitefish at least once per week?

○ No (<1 meal per week) ○ Yes (>= 1 meal per week)

If yes, how many times do you usually eat Lake Whitefish each week? _____

Off Season

Do you eat Lake Whitefish at least once per week when it is not in season?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you usually eat Lake Whitefish each week? _____

How do you usually prepare Lake Whitefish for eating?

○ Raw ○ Cooked ○ Dried ○ Smoked ○ Cured

Which parts of the fish do you eat? _____

Broad Whitefish

When are Broad Whitefish in season?

Where do you usually get Broad Whitefish from?

In Season

When in season, do you eat Broad Whitefish at least once a week?

○ No (<1 meal per week) ○ Yes (>= 1 meal per week)

If yes, how many times do you eat Broad Whitefish each week?

Off Season

Do you eat Broad Whitefish at least once per week when it is not in season?

○ No (<1 meal per week) ○ Yes (>= 1 meal per week)

If yes, how many times do you eat Broat Whitefish each week?

How do you usually prepare Broad Whitefish for eating?

○ Raw ○ Cooked ○ Dried ○ Smoked ○ Cured

Which parts of the fish do you eat?

Inconnu (Coney)

When are Inconnu (Coney) in season?

Where do you usually get Inconnu from?

In Season

When in season, do you eat Inconnu at least once per week?

○ No (<1 meal per week) ○ Yes (>= 1 meal per week)

If yes, how many times do you eat Inconnu each week?

Off Season

Do you eat Inconnu at least once per week when it is not in season?

○ No (<1 meal per week) ○ Yes (>= 1 meal per week)

If yes, how many times do you eat Inconnu each week?

How do you usually prepare Inconnu for eating?

○ Raw ○ Cooked ○ Dried ○ Smoked ○ Cured

Which parts of the fish do you eat?

Herring (Arctic Cisco)

When are Herring in season?

Where do you usually get Herring from?

In Season

When in season, do you eat Herring at least once per week?

○ No (<1 meal per week) ○ Yes (>= 1 meal per week)

If yes, how many times do you eat Herring each week?

Off Season

Do you eat Herring at least once per week when it is not in season?

○ No (<1 meal per week) ○ Yes (>= 1 meal per week)

If yes, how many times do you eat Herring each week?

How do you usually prepare Herring for eating?

○ Raw ○ Cooked ○ Dried ○ Smoked ○ Cured

Which parts of the fish do you eat?

Arctic Char

When are Arctic Char in season?

Where do you usually get Arctic Char from?

In Season

When in season, do you eat Arctic Char at least once per week?

○ No (<1 meal per week) ○ Yes (>= 1 meal per week)

If Yes, how many times do you eat Arctic Char each week?

Off Season

Do you eat Arctic Char at least once per week when it is not in season?

○ No (<1 meal per week) ○ Yes (>= 1 meal per week)

If yes, how many times do you eat Arctic Char each week?

How do you usually prepare Arctic Char for eating?

○ Raw ○ Cooked ○ Dried ○ Smoked ○ Cured

Which parts of the fish do you eat?

Arctic Grayling

When are Arctic Grayling in season?

Where do you usually get Arctic Grayling?

In Season

When in season, do you eat Arctic Grayling at least once per week?

○ No (<1 meal per week) ○ Yes (>= 1 meal per week)

If yes, how many times do you eat Arctc Grayling each week?

Off Season

Do you eat Arctic Grayling at least once per week when it is not in season?

○ No (<1 meal per week) ○ Yes (>= 1 meal per week)

If yes, how many times do you eat Arctic Grayling each week?

How do you usually prepare Arctic Grayling for eating?

○ Raw ○ Cooked ○ Dried ○ Smoked ○ Cured

Which parts of the fish do you eat?

Northern Pike (Jackfish)

When are Northern Pike in season?

Where do you usually get Northern Pike?

In Season

When in season, do you eat Northern Pike at least once per week?

○ No (<1 meal per week) ○ Yes (>= 1 meal per week)

If yes, how many times do you eat Northern Pike each week?

Off Season

Do you eat Northern Pike at least once per week when it is not in season?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Northern Pike each week?

How do you usually prepare Northern Pike for eating?

○ Raw ○ Cooked ○ Dried ○ Smoked ○ Cured

Which parts of the fish do you eat?

Pickerel (Walleye)

When are Pickerel in season?

Where do you usually get pickerel?

In Season

When in season, do you eat Pickerel at least once per week?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Pickerel each week?

Off Season

Do you eat Pickerel at least once per week when it is not in season?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Pickerel each week?

How do you usually prepare Pickerel for eating?

○ Raw ○ Cooked ○ Dried ○ Smoked ○ Cured

Which parts of the fish do you eat?

Burbot/Loche

When are Loche in season?

Where do you usually get Loche?

In Season

When in season, do you eat Loche at least once per week?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Loche each week?

Off Season

Do you eat Loche at least once per week when it is not in season?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Loche each week?

How do you usually prepare Loche for eating?

○ Raw ○ Cooked ○ Dried ○ Smoked ○ Cured

Which parts of the fish do you eat?

Lake Trout

When is Lake Trout in season?

Where do you usually get Lake Trout?

In Season

When in season, do you eat Lake Trout at least once per week?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Lake Trout each week?

Off Season

Do you eat Lake Trout at least once per week when it is not in season?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Lake Trout each week?

How do you usually prepare Lake Trout for eating?

○ Raw ○ Cooked ○ Dried ○ Smoked ○ Cured

What parts of the fish do you eat?

Bull Trout (Dolly Varden/Char)

When is Bull Trout in season?

Where do you usually get Bull Trout?

In Season

When in season, do you eat Bull Trout at least once per week?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Bull Trout each week?

Off Season

Do you eat Bull Trout at least once per week when it is not in season?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Bull Trout each week?

How do you usually prepare Bull Trout for eating?

○ Raw ○ Cooked ○ Dried ○ Smoked ○ Cured

Which parts of the fish do you eat?

Coho Salmon

When is Coho Salmon in season?

Where do you usually get Coho Salmon?

In Season

When in season, do you eat Coho Salmon at least once per week?

○ No (<1 meal per week) ○ Yes (>= 1 meal per week)

If yes, how many times do you eat Coho Salmon each week?

Off Season

Do you eat Coho Salmon at least once per week when it is not in season?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Coho Salmon each week?

How do you usually prepare Coho Salmon for eating?

○ Raw ○ Cooked ○ Dried ○ Smoked ○ Cured

Which parts of the fish do you eat?

Chinook Salmon

When is Chinook Salmon in season?

Where do you usually get Chinook Salmon?

In Season

When in season, do you eat Chinook Salmon at least once per week?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Chinook Salmon each week?

Off Season

Do you eat Chinook Salmon at least once per week when it is not in season?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Chinook Salmon each week?

How do you usually prepare Chinook Salmon for eating?

○ Raw ○ Cooked ○ Dried ○ Smoked ○ Cured

Which parts of the fish do you eat?

Chum Salmon

When is Chum Salmon in season?

Where do you usually get Chum Salmon?

In Season

When in season, do you eat Chum Salmon at least once per week?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Chum Salmon each week

Off Season

Do you eat Chum Salmon at least once per week when it is not in season?

○ No (<1 meal per week) ○ Yes (>= meal per week)

If yes, how many times do you eat Chum Salmon each week?

How do you usually prepare Chum Salmon for eating?

○ Raw ○ Cooked ○ Dried ○ Smoked ○ Cured

Which parts of the fish do you eat?

Big Eyed Herring (Least Cisco)

When is Big Eyed Herring in season?

Where do you usually get Big Eyed Herring?

In Season

When in season, do you eat Big Eyed Herring at least once per week?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Big Eyed Herring each week?

Off Season

Do you eat Big Eyed Herring at least once per week when it is not in season?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Big Eyed Herring each week?

How do you usually prepare Big Eyed Herring for eating?

○ Raw ○ Cooked ○ Dried ○ Smoked ○ Cured

Which parts of the fish do you eat?

Beluga Whale

When is Beluga Whale in season?

Where do you usually get Beluga Whale?

In Season

When in season, do you eat Beluga Whale at least once per week?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Beluga Whale each week?

Off Season

Do you eat Beluga Whale at least once per week when it is not in season?

○ No (<1 meal per week) ○ Yes (>=1 meal per week)

If yes, how many times do you eat Beluga Whale each week?

How do you usually prepare Beluga Whale for eating?

○ Raw ○ Cooked ○ Dried ○ Smoked ○ Cured

Which parts of the whale do you eat?

Food Frequency Questionnaire: General

Interview Date _____ Interviewer's Name _____

Participant's Name _____ Participant's ID _____

Fruits and Vegetables

1. On average, how many times do you eat fruit each week? _____
2. On average, how many times do you drink real fruit juice each week? _____
3. On average, how many times do you eat raw vegetables each week? _____
4. On average, how many times do you eat cooked vegetables each week? _____

Dairy

5. On average, how many times do you drink fresh milk each week? _____
6. On average, how many do you eat canned or packaged milk each week? _____
7. On average, how many times do you eat yogurt each week? _____

Pop

8. Do you drink pop? _____
   - 8a. On average, how many times do you drink non-diet pop each week? _____
   - 8b. On average, how many times do you drink diet pop each week? _____

Coffee and Tea

9. On average, how many cups of coffee do you drink per day? _____
   (Amount per week) _____
10. On average, how many cups of tea do you drink per day? _____
    (Amount per week) _____

Salt

11. On average, how many times do you eat salty snacks each week? _____
12. Do you usually add salt to prepared food? _____

13. Do you take any dietary supplements? _____
    - 13a. If yes, which supplements do you take? _____
    - 13b. How often do you take them? _____

Hair Prep Questions

Interview Date | Interviewer's Name

Participant's Name | Participant's ID

Do you dye your hair?

If yes, when is the last time you dyed your hair?

Have you gotten any permanent hair treatments?

If yes, what treatments have you gotten?

If yes, when is the last time you got the treatment?

For interviewer to fill out:

Approximate length of hair

Appendix 4: Results Letter

Dear <<NAME>>,

The results of your hair sample analysis are shown below, along with some information to help you interpret these results.

It is important to note that everybody has some level of mercury in their body. Lower levels of mercury are not known to be associated with any measurable health effects. However, the effects of exposure to low levels over long periods of time are not well understood. Exposure to very high levels of mercury, such as through industrial accidents, has been shown to cause damage to the kidneys, brain and the development of unborn babies.

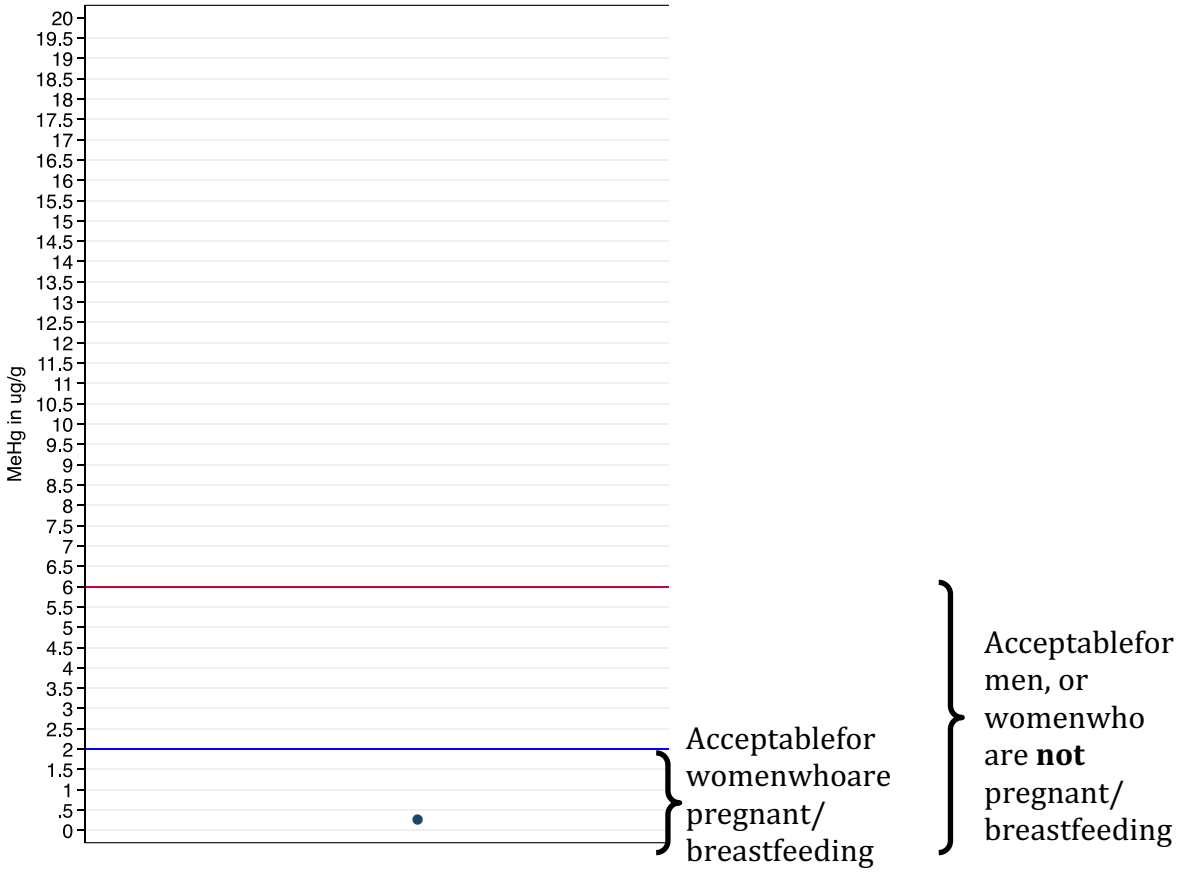
Health Canada has developed guidelines to help us decide whether the levels of mercury measured in a person put them at a higher risk for negative health outcomes. Given that we don't know everything about how low levels of mercury exposure can impact health over time, Health Canada took a cautious approach when developing these guidelines. Therefore, even at levels above the cut-points set out by Health Canada, we can't be sure that a person has any associated health problems. For this reason, health issues related to mercury exposure should **always** be diagnosed by a physician through a clinical exam. If you consented, a copy of this report was included in your health record so that your health care providers can use this information when monitoring your health.

Health Canada Guidelines:

- Levels below **2 µg/g** are acceptable for women who are pregnant or breastfeeding
- Levels below **6 µg/g** are acceptable for men, or women who are **not** pregnant or breastfeeding
- Levels between **6** and **20 µg/g** may be associated with an increased risk of health problems
- Levels above **20 µg/g** are more likely to be associated with an increased risk of health problems

Your Test Results: #. ## µg/g

- = Your Test Value



Your test results indicate that your risk of serious health effects from mercury exposure is low and no follow-up tests are required. I would like to take this opportunity to thank you for participating in this project. If you have any questions about these results, please contact Emily Walker toll free at 1-855-492-2525.

Sincerely,

Emily Walker

Appendix 5: Ethics Approval

Health Research Ethics Board

308 Campus Towers
University of Alberta, Edmonton, AB T6G 1K8
p. 780.492.9724 (Biomedical Panel)
p. 780.492.0932 (Health Panel)
p. 780.492.0459
p. 780.492.0629
f. 780.492.9429

Amendment Approval Form

Date:	September 19, 2016
Principal Investigator:	Karen Goodman
Study ID:	Pro00007868
Study Title:	Addressing Community Concerns about Risks from H. pylori Infection in the Circumpolar North
Sponsor/Funding Agency:	AHFMR - Alberta Heritage Foundation for Medical Research Alberta Cancer Foundation Alberta Innovates Health Solutions ArcticNet (NCE) CIHR - Canadian Institutes for Health Research Dalhousie University Circumpolar Boreal Alberta Research, Canadian Circumpolar Institute Nasivvik Centre for Inuit Health and Changing Environments - CIHR Network Environments for Aboriginal Health Research, Laval/Trent Northern Scientific Training Program, Indian and Northern Affairs Canada
Approval Expiry Date:	October 5, 2016

Thank you for submitting an amendment request to the Health Research Ethics Board - Biomedical Panel. The following have been reviewed and approved on behalf of the committee:

- Revised Manual of Procedures (Sep 2016);
- Mercury Exposure Consent Form (12 Sep 2016).

Note: Approval for an **amendment** does not change the original approval date of a study.

The membership of the Health Research Ethics Board - Biomedical Panel complies with the membership requirements for research ethics boards as defined in Division 5 of the Food and Drug Regulations and the Tri Council Policy Statement. The HREB - Biomedical Panel carries out its functions in a manner consistent with Good Clinical Practices and the Canadian General Standards Board (CAN/CGSB-101.1-2013).

Sincerely,

Donald W. Morrish, MD, PhD, FRCPC
Associate Chair, Health Research Ethics Board – Biomedical Panel

Note. This correspondence includes an electronic signature (validation and approval via an online system).

Appendix 6: Research Licenses

Yukon
Tourism and Culture
Box 2703, Whitehorse, Yukon Y1A 2C6

CULTURAL SERVICES BRANCH
HERITAGE RESOURCES UNIT

File No.: 6800-20-853

October 12, 2016

TO: Dr. Karen Goodman (University of Alberta)
Environment, Habitat Management (V-5R)
Lands Use Section, Lands Branch (K-320)
Health & Social Services (H-1)
ASTIS, Arctic Institute of North America
Vuntut Gwitchin First Nation

RE: **Dr. Karen Goodman (University of Alberta)**

Please be advised that the attached License has been issued under the Yukon Scientists and Explorers Act (1958).

Sincerely,

Jeff Hunston, Manager
Heritage Resources Unit

Enclosure

Yukon
Tourism and Culture

License Number: 16-78S&E

YUKON - CANADA
SCIENTISTS AND EXPLORERS ACT
LICENSE

PURSUANT to the provisions of the Scientists and Explorers Act (1958) of the Yukon, permission is hereby granted to:
Dr. Karen Goodman (University of Alberta)

to enter Yukon to conduct scientific research with respect to:

Investigating the Effect of Dietary Exposure to Mercury on the Severity of Chronic Inflammation and Gastic Neoplasia in Populations with an Elevated Risk of Gastric Cancer, Old Crow, Yukon.

GENERAL CONDITIONS

1. A complete, final report of the research conducted under this license shall be submitted, in duplicate, within one year of completion or termination of the project.
   a) A field or progress report as well as plain English summary, including descriptions or catalogues of collections made (where applicable) shall be submitted in duplicate on, or before, the expiry date written below.
   b) The Licensee shall provide a copy of any report or article published on the research conducted under this license to Heritage Resources Unit.

2. All camps shall be established according to the provisions of the Territorial Land Use Regulations.

3. All steps shall be taken to avoid unnecessary disturbance of wildlife.
   a) No camp site shall be established within 2 km of an active raptor nest.
   b) When using aircraft, maintain a minimum of 1,000 feet over wildlife such as sheep, raptor nests and migrating caribou.
   c) Pay particular attention to bear habitat, and take all steps necessary to avoid contact with bears such as use of bear fence, bear-proof containers and maintain a clean camp.
   d) All camps should be temporary/non-permanent with no structures, and entirely removed at the conclusion of the field work.

4. The Licensee shall meet with, inform and receive permission from First Nation(s) of the field activities conducted under this license on their settlement land(s), and shall not proceed if permission is not gained from the First Nation(s). The Licensee shall provide a copy of any report or article published on the research conducted under this license to the First Nation(s).

5. The Licensee shall strictly observe all applicable First Nation Settlement Land, Territorial and Federal legislation and regulations.

OTHER CONDITIONS:
NIL

THIS License is valid for the period **October 12th** to **December 31st , 2016.**

DATED at the City of Whitehorse, in the Yukon Territory, this **12th** day of **October**, A.D., **2016.**

Manager, Heritage Resources Unit
Cultural Services Branch
Tourism and Culture

Aurora Research Institute - Aurora College
PO Box 1450 Inuvik NT X0E 0T0
Phone: 867-777-3298 **Fax:** 867-777-4264 **E-mail:** licence@nwtresearch.com

July 06, 2016

Notification of Amendment

I would like to inform you that Scientific Research Licence No. 15785 issued to:

Dr. Karen J Goodman
University of Alberta
Division of Gastroenterology
7-142G Katz Group Building
Edmonton, AB
T6G 2E1 Canada
Phone: (780) 492-1889
Fax: (780) 492-7593
Email: karen.goodman@ualberta.ca

to conduct the following study:
Addressing community concerns about health risks from H. pylori infection

has been AMENDED to include the following activities.

SUMMARY OF AMENDMENT
The addition of two research components:

Traditional medicine component - The research team will interview participants to identify local medicinal plants and Indigenous approaches to managing H. pylori-related symptoms and disease. The team will collect traditional plants and associated traditional knowledge using existing community-based methods that have been identified through interviews, and will evaluate plant-based medicines for anti-H. pylori activity in the laboratory in Edmonton. A cross-generational knowledge exchange program will be designed and implemented to make sure the traditional knowledge be passed down from the elder/knowledge holders to youths in the community.

Mercury exposure component - The research team will collect hair samples from a subset of participants to develop a predictive model that estimates individual mercury exposure levels based on diet. The team will conduct a data analysis to estimate the effect of the individual mercury exposure level on the severity of inflammation of stomach tissues seen in H. pylori positive participants.

Please contact the researcher if you would like more information.

Sincerely,

Jonathon Michel,
Manager, Scientific Services

DISTRIBUTION
Aklavik Community Corporation
Beaufort-Delta Health and Social Services
Department of Health & Social Services - GNWT
Ehdiitat Gwich'in Council
Environmental Impact Screening Committee - c/o Joint Secretariat
Gwich'in Social and Cultural Institute

Appendix 7: Community Support Letters

VUNTUT GWITCHIN GOVERNMENT
Government of Vuntut Gwitchin First Nation
CHIEF AND COUNCIL
P.O. Box 94,
Old Crow, Yukon
Y0B 1N0
Phone: (867)966-3261
Fax: (867)966-3116
Web: www.vgfn.ca

August 22, 2016

Karen Goodman, PhD.
Professor, Department of Medicine &School of Public Health
Division of Gastroenterology
University of Alberta

Dear Dr. Goodman,

Re: The Old Crow *H. Pylori* Research Project

By means of this letter and on behalf of the Chief and Council of the Vuntut Gwitchin First Nation in Old Crow, Yukon, I am expressing our support for the research project proposed by your PhD student Emily Walker.

Our community continues to be concerned about the health risks associated with *H. pylori* infection. Results from this ongoing research have highlighted a higher-than-expected frequency of severe inflammation among participants from Old Crow who have the infection. For this reason, we support research aiming to learn more about factors associated with the severity of inflammation seen in our community. Specifically, we support the proposed investigation of the potential for mercury, an environmental contaminant found in fish, to contribute to the severity of inflammation of the stomach tissue seen in *H. pylori* positive community members.

Please contact the undersigned for further information.

Yours truly,

Bruce Charlie

Chief

AKLAVIK COMMUNITY CORPORATION
P.O. Box 119
Aklavik, NT X0E 0A0
Tel: (867) 978-2414 Fax: (867) 978-2815
Email: accmanager@northwestel.net

May 13, 2016

Karen J. Goodman, PhD.
Professor, Department of Medicine &School of Public Health
Division of Gastroenterology, 7-142 Katz
University of Alberta
Edmonton, AB
T6G 2E1

Dear Dr. Goodman,

The Aklavik Community Corporation fully supports the proposed *H. Pylori* research projects that have been of discussed at the Aklavik Health Committee at various meetings, the most recent being April 27, 2016. The Health Committee identified *H. Pylori* infection as a community health priority in 2004, because many Aklavik residents are worried about the serious health risks from this infection. The Health Committee has more recently requested the research team to study traditional medicines for their effectiveness in treating *h. pylori* infection and related stomach disease. The committee is also interested in pursuing research that aims to address the potential relationship between environmental contaminants like mercury and stomach health. We support both of these projects because they responds to the health concerns that the Aklavik residents would like health researchers and authorities to address.

Representative of the Aklavik Community Corporation will participate in planning the two research projects described above. We look forward to working with you on this important community health concern.

Sincerely,

Jordan McLeod
Chair
Aklavik Community Corporation

May 4, 2016

Karen Goodman, PhD.
Professor, Department of Medicine &School of Public Health
Division of Gastroenterology
University of Alberta

Dear Ms. Goodman,

Re: *H. Pylori* Research Project

On behalf of the Chief and Council of the Aklavik Indian Band, I am pleased to provide a letter of support from both the Aklavik Indian Band and the Ehdiitat Gwich'in Council who represent the Gwich'in of Aklavik.

Our community has always been concerned about the health risks associated with this infection and we fully support the following two research projects:
1) Exploration of how our traditional medicines might impact treating*H. pylori*infection and related disease.
2) Investigation of the potential for mercury, an environmental contaminant found in fish, to contribute to the severity of inflammation of the stomach tissue seen in *H. pylori* positive community members.

In addition, we support your initiative to fully involve not only adult community members in these projects but also our youth. We look forward to working with you on these important medical research initiatives for Aklavik.

Please contact the undersigned for further information.

Yours truly,

Aklavik Indian Band

Hamlet of Aklavik
Box 88, Aklavik, NT X0E 0A0
Ph: 867-978-2351
Fax: 867-978-2434

May 12, 2016

Karen J. Goodman, PhD
Professor, Department of Medicine & School of Public Health
Division of Gastroenterology
University of Alberta
Edmonton, AB
T6G 2E1

Dear Dr. Goodman;

The Council for the Hamlet of Aklavik supports your two (2) H.pylori research projects. We know the community residents are concerned about H. pylori and through your research projects we may get some answers to these concerns.

We support you working with community members, Elders, and youth to research our traditional ecological knowledge related to stomach illness and learn about the potential that our medicines may have in treating H.pylori infection and related disease. We also support research aiming to investigate the association between exposure to mercury through fish and sever inflammation of the stomach lining among H.pylori-positive people.
We hope this will help us better understand the ways that environmental contaminants may influence our stomach health.

If you require additional information, please contact me during regular working hours.

Yours in Community Health

William Storr
Deputy Mayor