Fish Consumption Advice for Alaskans

A Risk Management Strategy To Optimize the Public's Health

Ali K. Hamade, PhD, DABT
on behalf of the
Alaska Scientific Advisory Committee for Fish Consumption

Section of Epidemiology
Division of Public Health
Department of Health and Social Services
State of Alaska

Updated July 21, 2014

Acknowledgements:

The Section of Epidemiology would like to thank the many individuals who assisted in the development of this report. We particularly wish to acknowledge the contributions of the Alaska Scientific Advisory Committee for Fish Consumption members Jim Berner, Jay Butler, Bob Gerlach, Angela Matz, Joe McLaughlin, Todd O'Hara, and Chris Siddon. We thank Phil Davidson and Gary Myers from the University of Rochester, Sandrine Deglin from the Alaska Section of Epidemiology, Dariush Mozaffarian from Tufts University, Phil Spiller from the FDA, Lon Kissinger and Jeff Bigler from the EPA, and John Risher and Joe Sarcone from the Agency for Toxic Substances and Disease Registry for their helpful review comments. We also thank Stacey Cooper and Bezaleel Gebru for their help with the hair mercury Biomonitoring data, and Bezaleel Gebru for her help with literature search and review of socioeconomic changes in Alaska. Finally, we acknowledge Lori Verbrugge's efforts in developing the previous guidelines, which were helpful in developing the current guidelines.

Table of Contents

Report prepared by Ali K. Hamade, PhD, DABT on behalf of the Alaska Scientific Advisory Committee for Fish Consumption. This report includes materials from previous reports produced by the Alaska Division of Public Health.

Executive Summary

Benefits of Fish Consumption and Fishing

Extensive scientific research has documented the numerous health, social, cultural, and economic benefits of eating fish. Fish is an excellent source of lean protein, omega-3 fatty acids, antioxidants, and vitamins. A balanced diet that includes fish can lower the risk of heart disease and stroke. Fish is also an important part of a healthy diet for pregnant and nursing women, and children as the omega-3 fatty acids in fish improve maternal nutrition and brain development. Too little fish consumption by mothers may affect how children behave, learn, think and solve problems later in life, particularly when fish is replaced with low-nutrition foods. Neurodevelopmental benefits for omega-3 fatty acids are better established than the adverse effects of contaminants in fish.

In addition, many Alaskans, including Alaska Native people, have a strong reliance on fish as part of their traditional way of life and subsistence diet. Further, many Alaskans and non-Alaskans engage in recreational fishing that constitutes a huge industry supporting the Alaska economy. The benefits of fishing and fish consumption are not only economic, but also physical, cultural, and spiritual.

Risks of Fish Consumption

Fish can contain environmental contaminants they pick up from the water or sediments in which they live, or from the food they eat. Worldwide, the most notable fish contaminants are mercury, persistent organic pollutants (POPs), and biological toxins, such as saxitoxin and ciguatoxin. Mercury is a toxic metal that can damage the developing brain. Too much mercury may affect how children behave, learn, think and solve problems later in life. National studies have shown that all fish contain some mercury, with varying concentrations based on species, location, age, and other factors. POPs, which include polychlorinated biphenyls (PCBs), dioxins, organochlorine pesticides, and some polybrominated compounds, are toxicants that do not degrade rapidly in the environment or in the body. Adverse health effects associated with POP exposures may include hormone disruption, effects on learning and behavior, immune system suppression, or an increased risk of developing cancer. However, POP exposures from consumption of most Alaska fish are so low that any human health effects would be extremely subtle.

Monitoring in Alaska

To evaluate the safety of Alaska seafood, the Alaska Department of Environmental Conservation (ADEC) and the Alaska Department of Health and Social Services (DHSS) monitor contaminant levels in fish and human seafood consumers, respectively. ADEC began a comprehensive fish monitoring program in 2001 to analyze a wide variety of chemical contaminants in fish from Alaska, while DHSS began a Statewide Maternal Hair Mercury Biomonitoring Program in July 2002 to monitor the levels of mercury in the hair of pregnant Alaskans. Eligibility for this program has since been expanded to include all Alaskan women of childbearing age and, occasionally, men and older women.

Monitoring Results

Current data from Alaska's fish monitoring program demonstrate a wide range of mercury tissue concentrations among the 53 species of Alaska fish, shellfish, and mollusks sampled. Most species of Alaska fish – including all five wild Alaska salmon species – contained very low mercury levels that are not of health concern. However, a small number of Alaska fish species had high enough mercury levels to warrant recommendations for pregnant women, women of childbearing age that may become pregnant, nursing mothers, and young children to limit their consumption of those fish species.

Of 1145 women of childbearing age from 148 Alaska communities tested as part of Alaska's ongoing Statewide Mercury Biomonitoring Program through March 2014, only four (0.35%) had hair mercury levels that exceeded the 5 ppm threshold for public health concern (range: 5–8 ppm); eight women beyond childbearing years had hair mercury concentrations exceeding 5 ppm (range: 5–8 ppm). Follow-up data from some of these women showed that they consumed large quantities of fish and marine mammals that were known to be high in mercury.

Current data from Alaska's fish monitoring program demonstrate that all Alaska fish except salmon shark have levels of POPs that do not pose a health concern for consumers. Frequent consumption of salmon shark could be associated with elevated risk to health from PCB exposures.

Recommendations

Due to the numerous well-documented health and cultural benefits of fish consumption, adult men, and women beyond child-bearing years or who have had tubal ligations or surgeries removing the ovaries may continue unrestricted consumption of all fish from Alaska waters except salmon shark, for which moderate consumption is recommended. Pregnant women, women of childbearing age who may become pregnant, nursing mothers, and children aged <18 years may continue unrestricted consumption of fish from Alaska waters that are low in mercury, such as salmon, arctic cisco, big skate, black rockfish, broad whitefish, Dolly Varden, dusky rockfish, grayling, halibut <40 pounds, humpback whitefish, least cisco, lingcod <35 inches, Pacific cod, Pacific ocean perch, rainbow trout, rougheye rockfish, sablefish, sheefish, and walleye pollock.

To protect the nervous systems of developing fetuses and children, pregnant women, women of childbearing age who may become pregnant, nursing mothers, and children (defined as age <18 years) are advised to limit their consumption of lake trout, medium to large halibut (40–80 pounds), and medium-sized lingcod (35-40 inches length) to sixteen meals per month. These sensitive groups are advised to limit longnose skate, large halibut (80–140 pounds), and large lingcod (40–45 inches length) to twelve meals per month, and limit yelloweye rockfish, and very large halibut (140–220 pounds) to no more than eight meals per month. Pregnant women, women of childbearing age who may become pregnant, nursing mothers, and children aged <18 years are advised to limit their consumption of salmon shark, spiny dogfish, very large lingcod (≥45 inches), and extra-large halibut (>220 pounds) to no more than four meals per month. To simplify this advice, the Alaska Division of Public Health (DPH) developed a fish consumption calculator. Women of childbearing age and health care providers are encouraged to use this fish consumption calculator to inform their fish consumption choices and advice, respectively (DPH, 2014).

Most halibut guidelines apply only to large sport- or subsistence-caught fish, which can provide many meals to an individual consumer. In contrast, consumers that buy halibut from stores or restaurants would obtain each halibut meal from a different individual fish. The average commercially-caught halibut in Alaska in 2013 weighed 32 pounds, similar to previous years (IPHC, 2014b). The average weight for recreationally-caught halibut in Alaska ranged from 16 pounds to 22 pounds, and the average subsistence halibut in Alaska weighed on average approximately 24 pounds for the past few years (IPHC, 2014a). Thus, pregnant women, women of childbearing age who may become pregnant, and children aged <18 years can enjoy unrestricted consumption of most store-, recreational-, and subsistence-caught halibut from Alaska. Fishers who are concerned about mercury levels in the large halibut they catch (particularly ≥ 80 pounds) are encouraged to have their fish analyzed for mercury so that DPH can provide individualized advice about the maximum amount of that fish sensitive family members are can safely consume each month.

DPH also collaborated with the Agency for Toxic Substances and Disease Registry, the U.S. Fish and Wildlife Service, and the Bureau of Land Management to issue region-specific fish consumption advice based on assessments of contaminants in fish when exposure was deemed of potential public health concern. For example, an assessment of mercury in pike and burbot (lush) from the Middle Kuskokwim River area was used to develop region-specific fish consumption recommendations for women of childbearing age and children in various locations in this historic mining district, which has naturally high concentrations of mercury in bedrock and sediments. To minimize exposure to mercury and maximize the health benefits of fish consumption, women of childbearing age and young children living in communities in the Middle Kuskokwim River area are advised to eat more of the smaller fish and less of the larger and dried fish, as the latter are more likely to contain high mercury concentrations.

The current contaminant health risk assessment framework accepted by United States federal agencies often does not consider the benefits that co-occur with exposure to a contaminant (*e.g.*, benefits of fish intake associated with exposure to methylmercury). This aforementioned framework incorporates numeric factors that aim to account for uncertainties in extrapolation of findings from one human population to another or from animals to humans. However, because several uncertainties are associated with some toxicology and epidemiology studies that show only small undesirable effects of mercury from fish consumption and other studies show no such adverse effects, it is also important to consider the well-established and abundant benefits associated with fish consumption. These benefits are nutritional, cultural, spiritual, religious, physical, mental, and social, particularly in traditional and subsistence communities.

Recommendations and guidance on fish consumption may change as new data become available.

Purpose of Document

This document provides consumption guidance specific to Alaska-caught fish. The levels of mercury in Alaska-caught fish, as reported by the Alaska Department of Environmental Conservation (ADEC) Fish Monitoring Program up until 2013, are described and interpreted. Mercury is the contaminant that drives risk interpretation of fish consumption in Alaska. The risks of mercury exposure are weighed against the health benefits of fish consumption to develop fish consumption guidance that is both balanced and protective. Our intent is to assist individuals, families, and communities in Alaska as they make decisions about their fish consumption patterns. In addition, this document intends to assist health care providers in making dietary recommendations to all patients in general and to women of child bearing age in particular.

This document is not intended and should not be used to influence Air Quality or Water Quality criteria, or other related regulatory standards. The allowance of daily intake levels for mercury that exceed the reference dose established by the U.S. Environmental Protection Agency (EPA) should not be interpreted as a recommendation to relax air or water quality standards. The Alaska Division of Public Health (DPH) appreciates the health risks posed by mercury, and encourages regulatory agencies to control mercury releases to the fullest extent possible to protect our environment and the health of all Alaskans. DPH also recognizes the numerous natural and anthropogenic processes that make mercury available to fish.

History of Fish Consumption Advice in Alaska

Until 2007, DPH had recommended unrestricted consumption of all fish from Alaska waters. This recommendation was based largely on a combination of 1) insufficient fish contaminant data upon which to base restrictive advisories; 2) limited human mercury biomonitoring data that showed no exposures of health concern to Alaskans; and 3) the principle of nonmaleficence (*i.e.*, first do no harm). In this case, nonmaleficence refers to the potential harm that could occur by encouraging people to reduce their fish consumption and thereby not receive the beneficial health effects of this nourishing food (Egeland and Middaugh, 1997; Hibbeln et al., 2007).

In 2001, the United States federal government issued generic fish consumption advice that was contrary to DPH's longstanding recommendation. Due to concerns about mercury in fish, EPA and the U.S. Food and Drug Administration (FDA) recommended that pregnant women, women of childbearing age who may become pregnant, nursing mothers, and young children limit their consumption of fish. FDA recommended that these vulnerable members of the population should not eat shark species, swordfish, king mackerel or tilefish, and should limit consumption of other (commercial) fish to 12 ounces per week. EPA further recommended that these people should limit consumption of fish caught by family members and friends to one meal per week, and suggested finding alternative sources of protein for children. This federal guidance was edited and re-issued in 2004 as a joint EPA/FDA advisory (EPA/FDA, 2004). Most recently, EPA and FDA modified this guidance as discussed below.

Public health officials in Alaska reviewed the available evidence and concluded that the federal advice was inappropriate for Alaska. Alaskans rely heavily on fish as a lean, nutritious protein source, particularly among Alaska Native subsistence users who live in rural areas with less access to healthful alternative foods. Also, wild Alaska salmon, the fish most consumed by Alaskans, have far lower mercury levels than those used to develop the generic national guidelines.

In response to the national advisories in 2001, Alaska public health officials met with numerous stakeholders including tribal health corporations, other state agencies, and academic researchers to develop a consensus statement regarding fish consumption advice in Alaska. Because mercury levels in Alaska fish, particularly wild Alaska salmon, are far lower than those used to develop the generic national guidelines, the consensus statement considered the federal advice to be inappropriate public health policy for Alaska. The consensus statement reported that "the known benefits of fish consumption far outweigh the theoretical and controversial potential adverse health effects from mercury found in Alaska fish." DPH continued to strongly recommend that all Alaskans continue unrestricted consumption of fish from Alaska waters. However, the stakeholder group concluded that "an extensive collaborative program of research and monitoring of mercury in Alaska fish and in Alaskans who consume fish is needed and is being developed to increase the amount of data on mercury levels and follow trends in the future." (ADPH Bulletin, 2001)

In response to this charge for additional data, State agencies launched two major programs: ADEC began a comprehensive Fish Monitoring Program in 2001 to analyze a wide variety of chemical contaminants in fish from Alaska, and the Alaska Department of Health and Social Services (DHSS) began a Statewide Maternal Hair Mercury Biomonitoring Program in July 2002 to monitor the levels of mercury in the hair of pregnant Alaskans. This gave public health officials direct information about the degree of mercury exposure occurring in the most vulnerable subpopulation in Alaska, to optimally assess the likelihood of adverse health effects. This report presents and discusses both of these programs in detail. DPH also works closely with other researchers in the state to review study designs, ensure data quality and interpret study designs, and most importantly, provide public health advice.

In the summer and fall of 2006, ADEC provided a large body of data to DPH, describing the mercury content of over 2,300 individual fish from 23 species. Many species were confirmed to be low in mercury, whereas some species had mercury content of potential concern, prompting DPH to implement EPA's risk management principles (EPA, 1996). As part of this process, ADEC and DPH assembled a committee of scientific experts from Alaska to participate in the risk management process. This committee became known as the Alaska Scientific Advisory Committee for Fish Consumption.

The Alaska Scientific Advisory Committee for Fish Consumption met on November 30, 2006 and agreed that a few Alaska fish species had mercury levels too high to warrant "unrestricted consumption" guidance for the most sensitive members of the population, specifically women of childbearing age and children. They were not overly concerned, since human biomonitoring data indicated low mercury concentrations in hair. After considering the risks of mercury exposure, and the multiple benefits of fish consumption, the committee reached consensus on a strategy to provide balanced, yet protective, fish consumption advice, which was published on October 15, 2007.

Following the committee meeting, ADEC and DPH conducted a series of meetings and workshops with various stakeholders including DPH, ADEC, the Alaska Department of Fish and Game (ADF&G), the Alaska Seafood Marketing Institute (ASMI), Alaska Seafood Processors Advisory Committee (ASPAC), International Pacific Halibut Commission (IPHC), the Alaska Native Tribal Health Consortium (ANTHC), Aleutians Pribilof Island Association (APIA), University of Alaska, Alaska legislators, and sports fishing charter operators to obtain input.

By the end of 2013, ADEC had analyzed a total of 5907 fish representing 53 species. Based on these new data and on the need to provide fish consumption guidance that relied on state of the art findings in the mercury exposure and health effects field, the Alaska Scientific Advisory Committee for Fish Consumption initiated an evaluation of existing guidelines that considered both new fish contaminant concentrations and a weight of evidence assessment of methylmercury-associated health outcomes since the publication of the 2007 guidelines.

In June 2014, the EPA/FDA issued a draft update (Federal Register 79 FR 33559, Docket No. FDA-2014-N-0595) to their 2004 fish consumption advice. The proposed update encourages women and children to consume 8 ounces to 12 ounces of fish per week that are low in mercury for optimal nutritional benefits. The advice retains mercury level based limits on the consumption of certain fish that the FDA and EPA find to be high in mercury.

The final aspect of the consumption advisory process is the ongoing development and implementation of an effective public communications and education strategy. ADEC, DPH, the U.S. Fish and Wildlife Service (US FWS), the University of Alaska, and the ADF&G work together on this task.

Overview of Process for Developing Alaska's Fish Consumption Recommendations

EPA provides the states with guidance for collecting and interpreting environmental contaminant data in fish to assist with the development of fish consumption advice. ADEC uses Volume 1 of the guidance to perform fish sampling and analysis for the Fish Monitoring Program (US EPA, 2000). After ADEC receives and reviews the fish contaminant data, it forwards the data to DPH for interpretation of the health significance and development of optimal Alaska fish consumption recommendations.

DPH takes several steps to analyze the fish contaminant data and develop public health advice. First, the data are screened against EPA risk-based acceptable chronic daily intakes. We consider non-cancer risks potentially associated with chronic intake of a daily six-ounce meal of fish. These risk-based acceptable daily intakes of contaminants typically account for estimated or assumed uncertainties in the risk assessment process.

If a median chemical concentration for a fish species exceeds the non-cancer risk associated with consuming six-ounce daily meals on a chronic basis, DPH considers the risk in greater detail. This includes an examination of the evidence behind health-based risk values, the magnitude of safety factors that have been incorporated, and a consideration of the health benefits of fish consumption.

Screening criteria are limited to non-cancer health endpoints rather than cancer health endpoints. Most cancer risk screening criteria are based on animal cancer studies that usually involve administration of high doses of the test chemical, which may trigger mechanisms and risks not associated with lower doses (Pitot and Dragan, 1996; Klaunig, 2013). This mechanism of toxicity is not considered relevant to chronic low-dose exposures from consuming Alaska fish.

Purpose and Membership of the Alaska Scientific Advisory Committee for Fish Consumption

The purpose of the Alaska Scientific Advisory Committee for Fish Consumption (the Committee) is to provide scientific input and advice to DPH to assist with the development of optimal fish consumption recommendations for Alaska. Alaska scientists were selected for the Committee based upon their respective expertise in contaminants, human health, and nutrition, in the context of Alaska's unique social, cultural, economic, and geographical challenges. The membership roster was created during a joint meeting with ADEC and DPH staff members, and respective Division Directors (Table 1).

Table 1. Members of the Alaska Scientific Advisory Committee for Fish Consumption, 2014

Name	Organization	Expertise
James Berner, M.D.	Alaska Native Tribal Health Consortium	Pediatric medicine, contaminants
Jay Butler, M.D.	Alaska Native Tribal Health Consortium	Medical Epidemiology
Bob Gerlach, D.V.M.	Alaska Dept. of Environmental Conservation	Veterinary Medicine, Fish Monitoring
Ali Hamade, Ph.D.	Alaska Dept. of Health and Social Services	Toxicology
Angela Matz, Ph.D.	U.S. Fish and Wildlife Service	Environmental Toxicology, Fish and Wildlife Biology
Joe McLaughlin, M.D.	Alaska Dept. of Health and Social Services	Medical Epidemiology
Todd O'Hara, D.V.M., Ph.D.	University of Alaska Fairbanks	Environmental Toxicology
Chris Siddon, Ph.D.	Alaska Dept. of Fish and Game	Fish & Wildlife Biology

Description of the Alaska Fish Monitoring Program

The Fish Monitoring Program surveys selected marine and freshwater fish species from Alaska waters and tests these fish for a broad range of environmental contaminants. This program collaborates with biologists from ADF&G, the U.S. National Oceanic and Atmospheric Administration (NOAA), US FWS, IPHC, and commercial and Alaska Native fishermen.

Fish samplers are trained to perform the standard protocol written in the Quality Assurance Project Plan to assure submission of quality samples for analysis. Fish are caught, labeled, put in food grade plastic bags (fish sleeves or Ziploc® type bags) and placed in lined wetlock boxes. The samples are either immediately shipped on ice, or frozen and then shipped when feasible, to the Environmental Health Laboratories in Palmer or Anchorage.

For the fish samples available to date, the Environmental Health Laboratories processed the fish and performed chemical analysis on the homogenized skinless fillets of individual fish, testing for seven metals (arsenic, cadmium, lead, nickel, chromium, selenium, and methyl- and total- mercury).

Results for the heavy metal and mercury analyses can be found on the state web page: http://www.state.ak.us/dec/eh/vet/fish.htm.

Due to the high cost of organic contaminant analysis, the Environmental Health Laboratories analyzed only a subset of fish samples for organochlorine contaminants, including polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), polychlorinated dibenzo-p-dioxins (PCDDs) , polychlorinated dibenzofurans (PCDFs) and organochlorine pesticides (*e.g.*, “DDT”). This subset of fish does not include all species collected. AXYS Analytical Services Ltd. (AXYS) in British Columbia, Canada performed the testing following EPA analytical methods, and data were validated by independent contractors using EPA Region 10 Validation Methods.

Alaska-Specific Data Considered in the Development of Fish Consumption Recommendations

Alaska-specific data sources utilized in the decision-making process for the development of Alaska fish consumption recommendations include the following:

- ***Mercury levels in Alaska fish*** *(median, 95th percentile, maximum, trends by size for specific species)*
- ***Human biomonitoring*** *(levels of mercury in hair or blood from Alaskans)*
- ***Fish consumption rates in Alaska***
- ***Nutrition-related disease rates and trends in Alaska***
- ***Review of recent epidemiology studies of fish consumption and health endpoints***

Mercury levels in Alaska Fish

Data provided by ADEC in December 2013 included samples from 5,907 fish representing 53 different species caught in Alaska waters. Eight hundred eighty three (883) fish were collected at dockside from recreational fishermen, and 5,024 samples were collected from commercial fishermen or governmental fisheries biologists in areas where commercial harvest occurs. Each fish was analyzed separately for total mercury using combustion atomic absorption spectrometry (CAAS, Milestone DMA80 Direct Mercury Analyzer) according to EPA Method 7473. For each batch of 20 samples or less, a pair of Matrix Spike (MS) and Matrix Spike Duplicate (MSD) were run and every ten samples, a Certified Reference Material, a method blank and a sample duplicate were run.

At least 20 samples of most species were tested; however, fewer than 20 samples of several species, including kelp greenling (*Hexagrammos decagrammus*), rock greenling (*Hexagrammos lagocephalus*), Atka mackerel (*Pleurogrammus monopterygius*), copper rockfish (*Sebastes caurinus*), quillback rockfish (*Sebastes maliger*), silvergrey rockfish (*Sebastes glaucus*), yellowtail rockfish (*Sebastes flavidus*), red Irish lord (*Hemilepidotus hemilepidotus*), yellow Irish lord (*Hemilepidotus jordani*), northern rock sole (*Lepidopsetta polyxystra*), blue shark (*Prionace glauca*), Arctic char (*Salvelinus alpinus alpinus*), round whitefish (*Prosopium cylindraceum*), and longnose sucker (*Catostomus catostomus*). The number of fish needed to sufficiently represent the larger fish population is partially dependent on the variability of contaminant levels among these fish. The smaller the variability, the more certain we are that the levels of contaminants in fish fall within a defined range. The larger the variability, the less certain we are of that, and the more important the need for a larger fish sample size. The advisory board determined that for all fish species with fewer than 20 samples obtained, too few data existed upon which to base consumption advice at this time. After excluding these fish species, a total of approximately 3,622 fish representing 31 species were included in the final data set (Table 2). There were only 16 sheefish (*Stenodus leucichthys*) samples tested for mercury, but the advisory board decided to include these in the guidelines because of the low variability in mercury levels among these fish.

Table 2. Total Mercury in Alaska fish tissue, skinless fillets (parts per million, wet weight). Data from the Alaska Department of Environmental Conservation Fish Monitoring Program. 2013*

Species	N	Median (50th Percentile)	95th Percentile	Max.
Blue Mussels (*Mytilus edulis*)	24	0.013	0.050	0.053
Pink Salmon (*Oncorhynchus gorbuscha*)	186	0.013	0.26	0.36
Walleye Pollock (*Theragra chalcogramma*)	186	0.013	0.17	0.39
Bay Mussel (*Mytilus trossulus*)	23	0.014	0.050	0.053
Arctic Cisco (*Coregonus autumnalis*)	21	0.019	0.025	0.025
Weathervane Scallop (*Patinopecten caurinus*)	20	0.032	0.042	0.042
Sockeye Salmon (*Oncorhynchus nerka)*	249	0.038	0.060	0.082
Chum Salmon (*Oncorhynchus keta)*	290	0.039	0.064	0.10
Coho Salmon (*Oncorhynchus kisutch)*	327	0.039	0.061	0.11
Pacific Ocean Perch (*Sebastes alutus*)	78	0.041	0.16	0.26
Least Cisco (*Coregonus sardinella*)	26	0.045	0.093	0.098
Dolly Varden (*Salvelinus malma*)	22	0.058	0.55	0.55
Rainbow Trout (*Oncorhynchus mykiss*)	51	0.06	0.25	0.33
Chinook (King) Salmon (*Oncorhynchus tshawytscha*)	239	0.062	0.10	0.16
Humpback Whitefish (*Coregonus pidschian*)	98	0.066	0.14	0.18
Broad Whitefish (*Coregonus nasus*)	34	0.067	0.14	0.21
Dusky Rockfish (*Sebastes ciliatus*)	44	0.080	0.41	0.42
Arctic Grayling (*Thymallus arcticus*)	46	0.081	0.17	0.18
Black Rockfish (*Sebastes melanops*)	70	0.099	0.33	0.53
Pacific Cod (*Gadus macrocephalus*)	150	0.10	0.33	0.50
Sablefish (*Anoplopoma fimbria*)	243	0.11	0.58	1.2
Big Skate (*Raja binoculata*)	112	0.12	0.33	0.48
Rougheye Rockfish (*Sebastes aleutianus*)	38	0.12	0.62	0.87
Burbot (*Lota lota*)	27	0.25	0.84	0.85
Lake Trout (*Salvelinus namaycush*)	53	0.32	0.69	0.74
Northern Pike (*Esox lucius*)	575	0.33	0.93	1.4
Longnose Skate (*Raja rhina*)	114	0.37	0.76	1.0
Yelloweye Rockfish (*Sebastes ruberrimus*)	115	0.47	1.2	1.3
Spiny Dogfish (*Squalus suckleyi*)	66	0.73	1.2	1.3
Salmon Shark (*Lamna ditropis*)	95	1.3	1.9	2.1

** Halibut and lingcod data are presented according to weight and length in Tables 3a and 3b, respectively. See Appendix for region-specific recommendations and tissue mercury concentrations for Pike in Alaska. Targeted guidelines have been developed for communities that traditionally consume these fish on a regular basis (Appendix; DHSS, 2011).*
-N = Number of fish tested

Pacific halibut (*Hippoglossus stenolepis*) data from the Fish Monitoring Program were interpreted by weight class as calculated from total fish length (Table 3a). Despite substantial variability in mercury content within each weight class, the median mercury level increased with weight across all weight classes evaluated. Median mercury levels in the heaviest halibut (>200 pounds) were approximately 8-fold higher than those for the lightest halibut (<20 pounds). Because of this, the

Committee found it necessary to give halibut consumption advice specific to each weight class. Similarly, Alaska lingcod (*Ophiodon elongatus*) data were interpreted by length class (Table 3b) due to the trend of higher median mercury concentrations among longer fish.

Table 3a. Total mercury in Pacific Halibut skinless fillets by weight class (parts per million, wet weight). Data from the Alaska Department of Environmental Conservation Fish Monitoring Program, 2013.*

Weight, pounds	N	Median	Max	% fish containing >0.4 ppm	% fish containing >1.0 ppm	**Length, inches**
< 20.00	456	0.12	1.0	5.3%	0.0%	19–35
20.00–39.99	753	0.17	1.5	13.0%	1.5%	36–44
40.00–59.99	501	0.25	1.9	30.7%	4.2%	44–50
60.00–79.99	208	0.32	1.8	39.4%	7.7%	50–54
80.00–99.99	89	0.45	2.0	51.7%	16.9%	55–58
100.00–119.99	35	0.37	1.7	45.7%	17.1%	59–67
120.00–139.99	16	0.46	1.6	56.3%	31.3%	62–65
140.00–159.99	7	0.84	1.4	71.4%	28.6%	65–67
160.00–179.99	3	0.62	0.66	66.7%	0.0%	68–70
180.00–199.99	6	0.65	1.4	100.0%	16.7%	70–72
200.00–219.99	4	0.60	1.2	100.0%	25.0%	72–74
220.00–239.99	1	1.2	1.2	100.0%	100.0%	77
240.00–59.99	0	NA	NA	NA	NA	NA
260.00–279.99	1	0.57	0.57	100.0%	0.0%	80
280.00–299.99	2	1.1	1.3	100.0%	50.0%	80–82
300.00–319.99	1	1.2	1.2	100.0%	100.0%	84
320.00+	1	1.1	1.1	100.0%	100.0%	85

**Insufficient data were available to calculate a 95th percentile for all classes*

Table 3b. Total mercury in lingcod skinless fillets by length class (parts per million, wet weight), from the Alaska Department of Environmental Conservation Fish Monitoring Program, 2013. *

Length, inches	N	Median	Maximum	% fish containing >0.4 ppm	% fish containing >1.0 ppm
20.00–24.99	4	0.038	0.045	0.0%	0.0%
25.00–29.99	7	0.069	0.20	0.0%	0.0%
30.00–34.99	17	0.13	0.53	0.0%	0.0%
35.00–39.99	46	0.24	0.65	5.9%	0.0%
40.00–44.99	35	0.46	1.4	8.6%	5.7%
45.00–49.99	48	0.72	1.7	89.6%	10.4%
50.00+	12	0.76	1.0	100.0%	8.3%

** Insufficient data were available to calculate a 95th percentile for all classes*

Other researchers in Alaska also generate contaminant data for Alaska fish, including the University of Alaska Fairbanks, US FWS, Alaska Native tribes, and other entities. The Alaska Scientific Advisory Committee for Fish Consumption acknowledges the important contributions these research projects can make towards the development of fish consumption advice, and some of these data may be included in future updates to this DPH guidance. Inclusion of other data sources will require the Committee to establish guidelines for evaluation of data quality, representativeness, comparability of data type, and other criteria. These guidelines will allow the Committee to objectively determine which data are appropriate to merge with the ADEC Fish Monitoring data for the purpose of fish consumption guidance development.

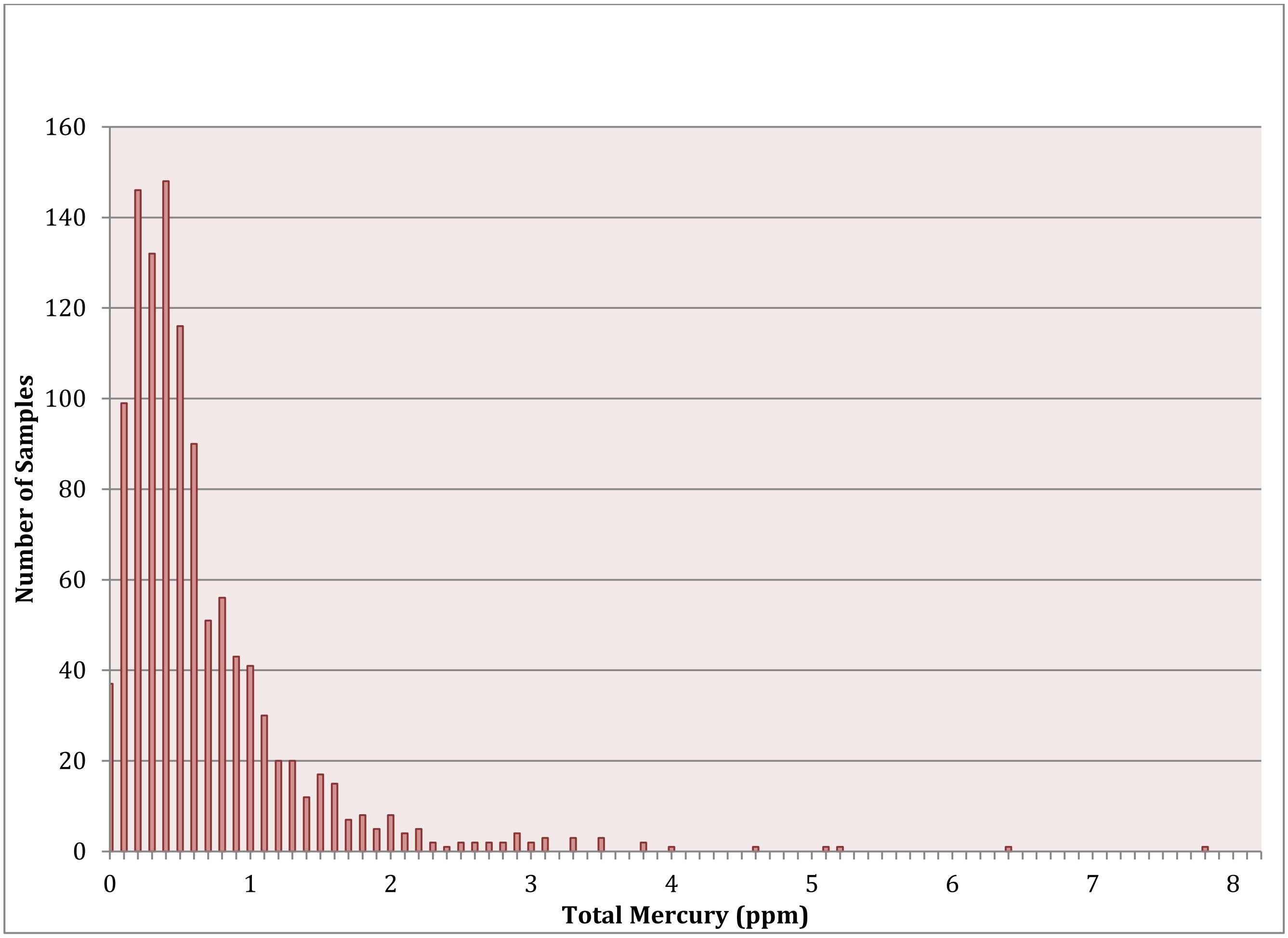
Human Biomonitoring (Mercury Levels in Human Hair or Blood)

Human biomonitoring is an important tool to assess actual human exposures to contaminants by measuring contaminant levels present in blood, urine, hair, fat, or other matrices. Biomonitoring data reduce scientific uncertainty relative to a standard risk assessment, which estimates human exposure to the contaminant from sources such as air, food, or water using a series of exposure assumptions and theoretical calculations. Alaska public health officials often use human biomonitoring data to optimize their risk interpretations and health advice regarding exposures to contaminants (Arnold *et al.*, 2005).

To assess mercury exposure in Alaska, DPH launched a Statewide Maternal Hair Mercury Biomonitoring Program in July 2002. This ongoing program originally offered free, confidential hair mercury testing to all pregnant women in Alaska. Eligibility has since been expanded to include all women of childbearing age (aged 15–45 years), and occasionally men and older women.

By the end of March 31st, 2014, hair samples from 1145 women of childbearing age from 148 Alaska communities were analyzed for mercury (ADPH data, unpublished). Participants included 339 pregnant women, 780 non-pregnant women of childbearing age, and 26 women of unknown pregnancy status. The participants had a median hair mercury level of 0.46 parts per million (ppm), with a maximum of 7.82 ppm (Figure 1). All hair mercury levels were well below 15 ppm, the lowest level from a study in the Seychelles islands, where people have fish consumption patterns very similar to Alaskans (van Wijngaarden *et al.*, 2006) that was not associated with adverse health effects in the offspring.

Figure 1. Hair Mercury Concentrations among Pregnant Women and Women of Childbearing Age (15–45 years; n=1145) — Alaska, July 2002–March 2014



To provide a margin of safety, DPH conducts follow-up investigations on all hair mercury levels at or above 5 ppm. Follow-up investigations were conducted for four women whose hair samples exceeded 5 ppm. All four women lived in the Yukon-Kuskokwim Delta or the Aleutian Islands and consumed large amounts of marine mammal livers or kidneys or large amounts of northern pike, which were determined to be the primary source of their mercury exposure. DPH informed the women of ways to reduce their mercury exposure if they chose to do so, by eating traditional foods that contain less mercury.

In addition to the Statewide Maternal Hair Mercury Biomonitoring Program, the Alaska Native Maternal Organics Monitoring (MOM) Study in the Yukon-Kuskokwim region (operated by ANTHC and the Yukon Kuskokwim Health Corporation) enrolled 250 mother/infant pairs, between 1999 and 2006. Maternal blood was obtained at the first prenatal visit, and the geometric mean of the maternal total blood mercury level for that group is 3.6 ppb of whole blood. The highest level recorded was 15 ppb (Dr. Jim Berner, ANTHC; personal communication – March 21, 2014). All blood mercury levels were well below that associated with subtle health effects in the children who had been exposed *in utero* (approximately 85 ppb in maternal blood based on data from the Faroe Islands epidemiological study) and levels associated with no effects in the Seychelles Island study (>15 ppm mercury in hair, equivalent to >60 ppb mercury in blood).

Fish Consumption Rates in Alaska

Fish consumption rates in human populations provide important information when developing fish consumption advice for those populations. Those rates allow public health officials to assess whether documented contaminant levels in fish might put consumers at risk, or if tissue concentrations are irrelevant because the item is rarely eaten.

Many Alaskans eat far more fish than the average American, especially in rural areas that rely on fish for subsistence (Nobmann *et al.*, 1992; Ballew *et al.*, 2004). Alaska is a large state with diverse ecological regions, and the people that inhabit these various ecological regions have different cultures and diets. These features present challenges to the comprehensive study of diets in Alaska.

The most recent well-designed effort to estimate fish consumption rates for Alaska communities comes from the Seldovia Village Tribe that conducted interviews with a statistically representative sample of residents from four villages in South Central Alaska (Seldovia, Port Graham, Nanwalek, and Tyonek) that are inhabited mostly by Alaska Natives. These interviews showed that the median fish consumption (not including shellfish) by a person who lived in these villages was 46.5 grams/day (12 ounces/week) for the year (or about 37.4 pounds per year). Median shellfish consumption was 3.3 grams/day (0.8 ounces/week). The 95th percentile fish and shellfish consumption rates in these villages were 247.1 grams/day (61 ounces/week) and 36.7 grams/day (9 ounces/week), respectively. Most fish consumed in these communities were salmon, followed by halibut. The survey respondents ate not only filet, but other parts of the fish as well, such as skin and belly flap (Merrill and Opheim, 2013).

An earlier effort, the Alaska Traditional Diet Survey (Ballew *et al.*, 2004), reported on questionnaire data collected in Summer 2002 to address traditional food consumption frequency, including fish, to fill the food consumption data gap in Alaska Native communities. In this survey, investigators interviewed participants from 13 villages and asked them to recall how often they ate specific food items over the previous twelve-month period, and their usual serving size for each item. Villages from five regional Tribal Health Corporations (Norton Sound Health Corporation, Yukon-Kuskokwim Health Corporation, Bristol Bay Area Health Corporation, Tanana Chiefs Conference, and Southeast Alaska Regional Health Consortium) participated in the survey.

The Alaska Traditional Diet Survey data was simplified by combining all the fish into two categories, salmon and non-salmon. In general, salmon was the most consumed fish. Median salmon and non-salmon consumption rates ranged from 26–61 pounds/year and 1–24 pounds/year, respectively. Survey respondents from Bristol Bay Region reported the highest median fish consumption rates (61 pounds/year for salmon and 24 pounds/year for non-salmon; 105.7 grams/day total fish; 26 ounces/week), while the respondents from the Tanana Chiefs in Interior Alaska reported the lowest median fish consumption rates (26 pounds/year of salmon and 1 pound/year of non-salmon; 33.6 grams/day total fish, approximately 8 ounces/week).

In contrast to fish consumption rates among rural subsistence consumers, fish consumption rates among urban Alaskans and non-subsistence consumers are less well characterized. Risk managers need to learn more about seafood consumption in urban centers in Alaska, including an assessment of the types, quantity, and mercury content of seafood consumed from sources outside Alaska.

Both of the aforementioned study outcomes present fish consumption rates that exceed both US EPA's (17 grams/day) and ADEC's (6 grams/day) rates that are sometimes used for setting environmental standards. ADEC is currently reassessing this rate for Alaskans in order to develop human health criteria for water quality standards. The fact that Alaskans consume large quantities of fish as compared to most other U.S. populations provides strong support for having stringent water quality criteria. This is because a higher fish consumption rate will naturally result in higher exposure to any contaminants in these fish.

Nutrition-related Disease Rates and Trends in Alaska

In communities that rely heavily on subsistence fish harvests – the great majority of which are populated mainly by Alaska Native people – traditional foods provide more than a food source. Subsistence is often a cultural cornerstone, providing spiritual, nutritional, medicinal, and economic well-being (van Oostdam *et al.*, 1999). Subsistence activities connect community members through work and through sharing, and provide a thread of cultural continuity from generation to generation. Therefore, any advice to limit traditional food consumption must be well-justified.

Unfortunately, the social and cultural disruption associated with food consumption advisories can have profound effects on the health and well-being of subsistence communities. For example, changes in diet, lifestyle, and the social and cultural disruption that follows alterations in subsistence traditions can contribute to a wide range of adverse health effects, such as increases in obesity, diabetes, hypertension, violence, alcoholism and drug abuse (Wheatley, 1994; Shkilnyk, 1985). Indigenous peoples in Canada have viewed chronic diseases as resulting from moving away from country (traditional) food and taking on the "white man's diet." (Kuhnlein *et al.*, 2001) This information indicates the importance of monitoring trends of nutritionally-related disease prevalence among subsistence communities to understand the potential health impacts of dietary changes.

DPH recognizes that fish consumption advisories may adversely affect all residents of subsistence communities. However, no easily accessible methodology exists to stratify populations based on their reliance on subsistence food. Because the majority of subsistence users in Alaska are Alaska Native people, as a rough proxy we compare outcomes among Alaska Native versus non-Native people. Increasing non-traditional food consumption and sedentary lifestyles among Alaska Native people have been associated with an increasing chronic disease prevalence, including an increase in hypertension and hypertensive disease mortality, glucose intolerance, and diabetes (Murphy *et al.*, 1997; Risica *et al.*, 2000a,b; Johnston *et al.*, 2011). Adult obesity, an important risk factor for these chronic diseases, has increased in prevalence in Alaska dramatically in recent years: from 49% in 1991 to 65% in 2011, representing a 30% increase within two decades (DHSS, 2014a) in Alaska Natives and non-Natives combined.

The prevalence of diabetes, which was once rare among Alaskan and Canadian Eskimos, has steadily increased (Scott and Griffith, 1957; Mouratoff *et al.,* 1967; Mouratoff and Scott, 1973; Schraer *et al.,* 1988; Schraer *et al.,* 2001). The increasing rate of diabetes is not limited to Alaska Native people, but also for all Alaskans. The prevalence of diabetes in the adult Alaska population increased from 41 per 1,000 population in 1996–1998 to 56 per 1,000 population in 2003–2005 (ADPH, 2007). In Alaska Native adults diabetes prevalence increased from 17.3 per 1,000 population in 1985 to 47.6 per 1,000 population in 2006 (Narayanan *et al.*, 2010).

The percentage of all Alaska adults categorized as overweight or obese has increased from 49% in 1991 to 65% in 2009 (DHSS, 2010). Fish consumption has been shown to reduce the occurrence of death from all causes (Gillum *et al.*, 2000), and many researchers have recommended maintaining or increasing fish consumption both for the cardiovascular disease prevention benefits as well as the benefits of preventing other chronic diseases (Dewailly *et al.*, 2002). In a cross-sectional study of 330 Yup'ik Eskimos, Makhoul *et al.* (2011) found that high concentrations of blood omega-3 fatty acids, EPA and DHA (found in fish and marine mammals), were associated with lowered dyslipidemia and lowered systemic inflammation among overweight and obese people. In a similar study that drew associations between diet and blood chemistry measurements in 530 Yup'ik Eskimos aged 14–94 years old, traditional food intake was significantly positively associated with high-density lipoprotein cholesterol (HDL or "good cholesterol") concentration and significantly negatively associated with triglyceride concentration (Bersamin *et al.*, 2008).

Alaska Native people previously had a lower risk for death from coronary heart disease than did Alaskans of other races. Over the past several decades, this discrepancy has disappeared (McLaughlin *et al.*, 2004). The higher rates of heart disease are due to the higher prevalence of risk factors for coronary heart disease among Alaska Native people in recent years. Tobacco smoking rates are very high in Alaska Native people, store-bought foods have replaced traditional foods in the diet to varying extents, and modern conveniences such as motorized vehicles have led many Alaska Native people to a more sedentary lifestyle (Ebbesson *et al.*, 2005). Thus, the changing patterns of disease in Alaska Native people likely reflect increases in smoking, decreases in physical activity, changes in dietary practices, and increased obesity (Middaugh, 1997a,b).

During the period 1981–2007, hypertensive heart disease mortality increased 155% among Alaska Native people over the age of 35 years, while it increased only 13.7% for US whites in the same age range (Johnston *et al.,* 2011). In addition, age-specific heart disease mortality was almost identical between US whites and Alaska Natives aged 35–74 years, but 30% lower for Alaska Natives as compared to U.S. whites aged 75 years or older. The authors hypothesized that the healthy lifestyle of older Alaska Natives may account for the discrepancy in age-specific rates as compared to the younger cohort. This hypothesis is supported by data from Nobmann *et al.* (2005) who found that the diet of elderly Alaska Natives was more traditional and contained more unsaturated fatty acids, mainly from salmon and seal oil sources, than the diet of younger adults. Age-adjusted heart disease mortality rate was consistently 20% lower in Alaska Natives than US whites from 1981 through 2007.

The Education and Research Towards Health (EARTH) study is a 5-year prospective study of American Indians and Alaska Natives that aims to evaluate the potential associations between diet, physical activity, and other lifestyle and cultural factors and the development and progression of chronic diseases (Slattery *et al.*, 2007). Schumacher *et al.* (2008) evaluated data from the EARTH study and reported that 48% of Alaska Native men and 40% of Alaska Native women in 26 villages and communities in three Alaska regions had elevated blood pressure.

As recently as the 1950s, it was believed that hypertension was an uncommon occurrence in Alaska Native communities. However, a study conducted in 1987–1988 in 15 Alaska Southwestern villages found hypertension in 24% of the population (Murphy *et al.*, 1997) and that was associated with overweight, non-indigenous diet, mechanized activities, and glucose intolerance. Johnston *et al.* (2011) expressed concern that high rates of metabolic syndrome reported in the EARTH study (26% men, 31% women; Schumacher *et al.*, 2008) and unhealthy lifestyles could be the reason for higher heart disease morbidity and mortality. Schumacher *et al.* (2008) found that the most common component of metabolic syndrome among US white men and Alaska Native men was high blood pressure.

Homer *et al.* (2009) evaluated stroke mortality among Alaska Natives and found that the rate did not significantly decline over the duration of this study (1984–2003) in contrast to that of U.S. whites, which decreased significantly. Notably, the stroke mortality rate among Alaska Natives was significantly elevated from 1994–2003 as compared to U.S. whites, but not in the previous decade, 1984–1993. The authors also reported that stroke mortality was more prevalent in Alaska Natives under 45 years of age as compared to older US whites and older Alaska Natives (Homer *et al.*, 2009). The authors hypothesized that the observed stroke mortality among Alaska Native people likely reflects substantial lifestyle changes over the past decades, particularly the gradual shift from traditional foods and lifestyle towards a Westernized diet and lifestyle (Homer *et al.*, 2009).

The observed decline in health indicators associated or co-occurring with a shift away from a traditional diet and lifestyle requires further examination and evaluation.

Review of recent epidemiology studies of fish consumption and health endpoints

Since the previous Alaska fish consumption guidelines, there have been many studies that evaluated a potential association between fish or mercury exposure and health outcomes. The most sensitive endpoints are neurodevelopmental. Recently, there have been concerns of cardiovascular effects and diabetes incidence in adults associated with mercury exposure from fish consumption. In addition to reviewing studies that evaluated methylmercury-neudevelopmental associations, we briefly review select studies that evaluated potential associations between mercury exposure from fish and both diabetes and cardiovascular outcomes.

Neurodevelopmental Endpoints

The critical target organ for methylmercury toxicity is currently accepted to be the central nervous system. Three acute, high-dose poisoning episodes that occurred in Japan and Iraq during the period from 1953 through 1972 elucidated the severe, toxic effects of ingested methylmercury (Kutsuna, 1968; Kinjo *et al.*, 1995; Bakir *et al.*, 1973). These outbreaks occurred with extremely high exposures to mercury and resulted in death or severe, irreversible neurological damage. Investigators also noted milder toxic effects. The most susceptible subpopulation to the nervous system effects of methylmercury is the developing fetus as it largely retains the mercury it takes from its mother and has a developing nervous system that is more susceptible to methylmercury than that of adults.

The exposure of Alaskans to methylmercury through fish consumption is extremely small compared to these aforementioned high-dose poisoning episodes in Japan and Iraq. Health effects of very low-dose mercury exposure from fish consumption, if any, are likely to be unmeasureable and of much less importance than many other variables that may impact neurological outcomes in children, such as pre-term birth, abuse and neglect, lower parental educational attainment, prenatal maternal alcohol and other drug use, and other factors. This is true even among the most sensitive segment of the population to the neurotoxic effects of methylmercury, the developing fetus.

Several large-scale epidemiologic studies, as well as many small studies, have examined the potential association between chronic low-level *in utero* exposures to mercury from fish and or marine mammal ingestion and subtle neurodevelopmental effects. The most influential studies for deriving fish consumption guidelines worldwide are those of the Seychelles Islands and the Faroe Islands. The Seychelles Islands are off the coast of Africa, north of Madagascar, and the Faroe Islands are in the North Atlantic between Scotland and Iceland. Because of the large sample sizes, the rigorous intensive follow-up testing, and the homogeneous nature of both study populations, the studies provide the best opportunity to characterize the magnitude and nature of the risks potentially associated with low-level methylmercury exposure through fish and/or marine mammal consumption. The initial studies have been reviewed and analyzed elsewhere (NRC, 2000; NIEHS, 1998). The results are summarized briefly here.

The Seychelles

In 1989, the University of Rochester, in collaboration with the Seychelles Island Government, initiated a large scale study (the Seychelles Child Development Study) of 779 mother-infant pairs, examining the developmental effects of low-level methylmercury exposure through frequent fish consumption (Cernichiari *et al.*, 1995; Davidson *et al.*, 1995, 1998; Marsh *et al.*, 1995; Shamlaye *et al.*, 1995). Seventy-five percent of the women indicated eating 10-14 fish meals per week (Shamlaye *et al.*, 1995). Mercury levels in 20 different species of fish (homogenized muscle) ranged from 0.001 ppm for reef fish to 2.04 ppm for Moro shark, and 4.4 ppm for dog tooth tuna (Cernichiari *et al.*, 1995). The overall average fish muscle tissue concentration was 0.3 ppm. Multiple maternal hair samples were collected during pregnancy for quantification of methylmercury exposures. Maternal hair mercury levels in the Seychellois cohort mothers were as high as 27 ppm with a median of 6.6 ppm (compared to a maximum of 7.82 ppm and median of 0.47 ppm in 1145 women of childbearing age in Alaska; this median hair level was more than ten times lower than the Seychelles median). All but two women in the initial cohort study had hair concentrations <20 ppm, and 659 (80% of the cohort) had maternal hair concentrations ≤12 ppm. Maternal hair concentrations did not vary during pregnancy. Maternal hair mercury levels in each trimester correlated with levels representing the entire gestational period, indicating no seasonal differences or peak exposure periods.

Numerous neurodevelopmental tests and physical examinations were conducted on the children at 6.5, 19, 29, and 66 months of age. The neurologic evaluation included the Fagan Test, the Revised Denver Development Screening Test, the Bayley Scales of Infant Development, the General Cognitive Index, the Infant Behavior Record, Mental Developmental Index, McCarthy Scales of Children's Abilities, Psychomotor Developmental Index, Preschool Language Scale, and numerous other perceptual, verbal, memory, behavior and motor tests.

No adverse health effects resulting from prenatal or postnatal exposure to methylmercury were noted in the 66-month evaluation, or in any of the earlier tests (Davidson *et al.*, 1998). In fact, greater prenatal and postnatal exposure to methylmercury correlated with better performance on some test scores, an outcome that may have resulted from beneficial effects of increased fish consumption.

In a follow-up of this cohort at age 9 years, domain-specific tests previously reported to show an adverse association with prenatal exposure to methylmercury in the Faroe Islands were used (Myers *et al.*, 2003). Investigators tested cognition (memory, attention, executive functions), learning, perceptual, motor, social and behavioral abilities. Of the 21 end-points evaluated, only two showed a significant association with prenatal exposure. One association was adverse (the grooved pegboard, non-dominant hand) and the other association was beneficial (Conner's Teacher Rating Scale, ADHD Index). The authors noted several outliers for the aforementioned endpoints that had both <7.5 ppm prenatal maternal hair mercury concentration and lower test performance results.

It is important to note that the Boston Naming Test that was negatively-associated with higher prenatal mercury exposure in the Faroe Islands study (discussed below) and the critical endpoint upon which the current EPA Reference Dose is based, was not significantly correlated with prenatal mercury exposure in the Seychelles study. The authors also noted that the Boston Naming Test is affected by cultural variation and that Seychellois children performed lower than US children, on average (Myers *et al.*, 2003).

As predicted, effects from other covariates known to affect child development were found. Consistent with the previous evaluations of this cohort, the investigators concluded that the findings did not support an association between prenatal exposure to methylmercury from consumption of large quantities of a wide variety of ocean fish and adverse neurodevelopmental consequences (Myers *et al.*, 2003). Additional testing of the cohort at 107 months using the "Child Behavior Checklist" (CBCL) suggested that there was no association between prenatal mercury exposure and "Social Problems and Somatic Complaints", although there was an association between postnatal mercury exposure above 8 ppm in children and "Thought Problems" (Myers *et al.*, 2004). The authors concluded that there was no clear pattern between both prenatal or postnatal mercury exposure and behaviors measured by the CBCL. A more detailed analysis of postnatal mercury exposure by the authors found, for the most part, no association with neuropsychological test performance. The authors found mixed results from different tests that evaluated the same neuropsychological endpoint/domain, such as fine motor coordination (adverse association with the Grooved Pegboard test, but no associations with either Finger Tapping or Trail Making tests) (Myers *et al.*, 2009).

Subsequent testing of this cohort at 17 years of age focused on 27 behavioral and cognitive outcomes with tests that included the Wisconsin Card Sorting Test, the California Verbal Learning Test, the Woodcock Johnson Achievement Test, measures of problematic behaviors, and subsets of the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Davidson *et al.*, 2011). The authors reported no association between prenatal mercury exposure and 21 of the tests. In fact, the authors reported desirable associations between increasing prenatal mercury and several test performances including calculation in the Woodcock Johnson test, fewer number of trials to complete the CANTAB test, fewer reports of substance use, and incidents of and referrals for problematic behaviors at school. One adverse association was reported between prenatal mercury and the likelihood of having 1–3 referrals (55 children group size) to a school counselor as compared to no referrals (237 children group size). However, this association was not present when the number of referrals considered was 4–12 (48 children group size) or >13 (31 children group size).

A recent assessment of neurodevelopment and behavior in the Seychelles study included 533 participants from the initial cohort (van Wijngaarden *et al.,* 2013) and evaluated associations between both prenatal and recent postnatal mercury exposure and Profile of Mood States – Bipolar (POMS-Bi), Finger Tapping, Kaufmann Brief Intelligence Test (K-BIT), measures of fine motor control and complex perceptual motor control, visual spatial contrast sensitivity. The authors found no association between prenatal mercury exposure and any of the test battery components. However, recent postnatal mercury exposure was adversely associated with Finger Tapping (nondominant hand) among women but not men, and with K-Bit in the entire cohort (van Wijngaarden *et al.*, 2013).

Overall, the vast majority of developmental and behavioral tests were not associated with prenatal or postnatal mercury exposure in Seychellois children. However, some tests showed favorable associations with mercury exposure, while others showed adverse associations. The favorable associations with mercury exposure may well be indicative of the benefits of fish consumption as an excellent source of protein, polyunsaturated fatty acids, selenium and other nutrients.

The Faroe Islands

The other large-scale study took place in the Faroe Islands, where methylmercury exposure occurred primarily through consumption of pilot whale meat (1–2 meals a week) containing an average total mercury concentration of 3.3 ppm (1.6 ppm methylmercury) (Grandjean *et al.*, 1994). Of 1,023 consecutive births, the median umbilical cord blood-mercury concentration was 24.2 ppb; 25.1% (n=250) had blood-mercury concentrations that exceeded 40 ppb. The median maternal hair mercury concentration was 4.5 ppm, with 12.7% (n=130) of women having concentrations exceeding 10 ppm (Grandjean *et al.*, 1992).

Evaluation of 583 subjects during infancy (age <12 months) demonstrated that infants with higher hair mercury concentrations had more rapid achievement of developmental milestones than other infants (Grandjean *et al.*, 1995). The authors suggested that this desirable association was potentially confounded by breast feeding, particularly as increased frequency of breast-feeding was associated with better test performance and higher hair mercury concentrations (Grandjean *et al.*, 1995).

Possible *in utero* neurologic effects were subsequently evaluated at 7 years of age (Grandjean *et al.*, 1997). Neurologic and developmental tests included the Neurobehavioral Evaluation System (NES) Finger Tapping Test, the NES Hand-Eye Coordination Test, NES Continuous Performance Test, the Tactual Performance Test, the Boston Naming Test for language skills, the Wechsler Intelligence Scale for Children-Revised (WISC-R), WISC-R Digit Spans, WISC-R Block Designs, WISC-R Similarities, Bender Gestalt Test for visuospatial skills, California Verbal Learning Test for memory, and the Nonverbal Analogue Profile of Mood States. Analyses of 917 children at 7 years of age found no clinical or neurophysiological mercury-related abnormalities (Grandjean *et al.*, 1997). However, subtle decreases in neuropsychological test performance, particularly in the language, attention, and memory domains, were associated with prenatal mercury exposure in both the whole cohort and the cohort subset that had maternal hair levels below 10 ppm, although, as the authors reported "test scores obtained by most of the highly exposed children were mainly within the range seen in the rest of the children...." (Grandjean *et al.*, 1997). Moreover, when PCBs were considered in the model, three of the four associations between prenatal methylmercury exposure and the aforementioned neuropsychological tests lost statistical significance, suggesting that PCBs may potentiate the effect of methylmercury on neurodevelopment. Interestingly, the Faroese children had excellent visual contrast sensitivity that could possibly be attributed to the ample supply of dietary omega-3 fatty acids.

In a follow-up at 14 years of age, Debes *et al.* (2006) evaluated neuropsychological testing in this cohort. Members of the initial cohort (878 children) underwent the examination based on the same test battery conducted at 7 years of age by Grandjean *et al.* (1997). The authors reported no effect of recent postnatal mercury exposure on any outcomes in the test battery; however, they found that prenatal mercury exposure was associated with subtle deficits in finger tapping speed, reaction time on a continued performance task, and cued naming. To illustrate the subtlety of some of these associations, the magnitude of adverse outcomes ranged from 6% to 10% of the *standard deviation* of test scores for a ***doubling*** of hair mercury concentration. In the Boston Naming Test (with cues), this magnitude was approximately 0.3 points or approximately 0.7% of the mean score for all children tested (Debes *et al.*, 2006). The authors also found desirable performance outcomes, such as better scores on the WMS-II Spatial Span test, significantly associated with higher prenatal mercury exposure. The study included three main measures of prenatal mercury exposure, maternal hair, cord blood, and cord tissue. However, associations between test performance and exposure measures were not always consistent. At age 14 years, Murata *et al.* (2004) also reported an association between prenatal methylmercury exposure and delays in the response of the brain to sound; however, hearing thresholds were not affected by this exposure.

In addition to high mercury concentrations, pilot whales also contain relatively high concentrations of PCBs and organochlorine pesticides. In 2001 Grandjean, *et al.* (2001), reported neurobehavioral deficits associated with PCBs in this cohort. PCBs were quantified by multiplying the sum concentration of 3 congeners by 2 to derive the total. This is a relatively crude method with which to quantify PCBs; more rigorous methods quantify many more congeners (typically 40 or more; 209 are possible) and sum them for a more accurate total. Such analyses allow consideration of structure-activity relationships of individual congeners, and increase power to detect significant associations with outcome variables (McFarland *et al.*, 1989). Four of the neuropsychological outcomes measured showed possible decrements associated with wet-weight PCB concentration, but not lipid-adjusted PCB concentrations. Adjustment for methylmercury reduced the association to a statistically insignificant level. The strongest PCB effect was noted in those within the highest tertile of methylmercury exposure. Interestingly, the most sensitive parameter to the PCB exposure was the Boston Naming test, the endpoint selected by EPA to derive its reference dose for methylmercury. EPA concluded that "…methylmercury neurotoxicity may be a greater hazard than that associated with PCBs, but PCBs could possibly augment the neurobehavioral deficits at increased levels of mercury exposure." Previous statistical analysis by this group indicated methylmercury-associated neurobehavioral deficits were unlikely to be affected by PCB exposure (Budtz-Jorgensen *et al.*, 1999). This suggests that certain agents may confound the mercury-neurodevelopment association. Another important potential confounder in the Faroe Islands study was socioeconomic status, which the study did not account for.

Other Studies

One of the largest cohort studies that examined the potential effect of prenatal methylmercury exposure on neurodevelopment consisted of 10,970 New Zealand women who had given birth in 1977 and 1978 (Crump *et al.*, 1998). The study authors collected hair samples and administered dietary questionnaires to these women. Two hundred and thirty seven child-mother pairs were included in the final study cohort. The cohort participants were then classified into three groups by maternal hair mercury concentration, >6 ppm, 3–6 ppm, and 0–3 ppm. A major source of mercury in this cohort was shark meat (in "fish and chips"), which notoriously contains elevated concentrations of mercury and possibly many POPs as well. In 1985, a test battery of 26 psychological and scholastic tests was administered to the children at ages 6–7 years. The study authors used five tests to calculate a benchmark dose (defined below) that would constitute a "no observed adverse effect level" (NOAEL) at or below which no adverse mercury effects are expected. The authors' most conservative interpretation of these data yielded a mercury concentration in hair that ranged from 7.4 ppm to 10 ppm.

A study by Sagiv *et al.* (2012) evaluated associations between each of prenatal exposure to mercury (median maternal hair mercury, 0.45 ppm; range, 0.03–5.14 ppm) and maternal fish consumption and attention deficit/hyperactivity disorder-related behavior in children born in New Bedford, Massachusetts between 1993 and 1998. The cohort members were also exposed to PCBs through fish. The study authors reported benefits for these endpoints with consuming more than two servings of fish per week as compared with consuming fewer than two servings per week. Stronger beneficial associations were observed after adjusting for mercury intake, but adverse outcomes were associated with mercury exposure of >1 ppm in maternal hair as compared to mercury exposure <1 ppm in maternal hair. The adverse association with mercury was unaffected after adjusting for fish consumption. These results show the potential for neurodevelopmental toxicity from ingesting methylmercury, although the toxicity appears to be eliminated with the consumption of fish, particularly in women who consumed more than 2 servings of fish per week.

A series of studies also evaluated associations between neurodevelopmental outcomes and prenatal and postnatal exposure to omega-3 fatty acids, mercury, and PCBs in school-aged Inuit children from Nunavik (Arctic Quebec) in Canada (Boucher *et al.*, 2010, 2011, 2012a, 2012b). Exposure to omega-3 fatty acids and contaminants was assessed in the mothers at birth and in the children at 11 years of age. Boucher *et al.* (2010) evaluated potential associations between these exposures and information processing ability as assessed with event related potentials (ERPs) in 118 children (mean maternal blood mercury = 21.5 μg/L; mean child blood mercury = 4.7 μg/L). The authors reported no postnatal effects of mercury or PCBs, but found some effects associated with maternal PCBs and mercury exposure. These associations were only observed in children who had breastfed for <3 months, but not in those breastfed for >3 months.

Boucher et al (2012a) did not find an association between adverse neurodevelopmental outcomes and postnatal current exposure (mean ~ 1 ppm in hair) or PCBs exposure (mean = 73.7 μg/kg fat in blood) in a group of 279 11-year-old children, although blood lead level (mean = 2.7 μg/dL) was adversely associated with externalizing problems. Only cord blood mercury (prenatal; equivalent to >2.5 ppm in maternal hair) exposure, but not PCB or lead, was marginally significantly associated with attention problems and ADHD behavior in children, although it was not associated with internalizing or externalizing problems. However, the lead exposure in utero appeared to have a much larger effect on children than did mercury and confounded the mercury effect below 22.9 μg/L mercury in cord blood (~5 ppm in maternal hair). This suggests that lead or other unmeasured agents or conditions could potentially confound a methylmercury association with neurodevelopmental outcomes.

Subsequently, Boucher *et al.* (2012b) examined ERPs in 196 children and found an association between postnatal current lead exposure at 11 years of age (mean = 2.6 μg/dL) and deficits in response inhibition as in the previous study (Boucher *et al.*, 2010). The authors also reported adverse associations with postnatal current PCB-153 (mean = 72 μg/kg fat in blood) but not with current mercury exposure (mean 4.6 μg/L in blood; ~ 1 ppm in hair). The same research group (Boucher *et al.*, 2011) found beneficial effects of prenatal omega-3 fatty acids, regardless of contaminant concentrations, on memory function in this cohort that included 154 children (mean age = 11 years). Omega-3 fatty acid desirable effects were not apparent with high PCB and mercury concentrations, although no adverse effects of contaminants were evident either.

Summary of Neurodevelopmental Endpoints

The Alaska Scientific Advisory Committee for Fish Consumption reviewed several studies, including those summarized above, and decided that the Seychelles Islands study provides the most appropriate data for determining the neurodevelopmental human health risks posed by mercury exposure via fish consumption in Alaska. The Seychelles Islander and Alaskan exposure scenarios are comparable, as both populations eat large quantities of ocean fish that have similar mercury levels that encompass a similar range in the two locations as well as lower POP levels than in the Faroe Island fish and pilot whale. We conclude that the Seychelles Islands study provides the most appropriate data to develop an Alaska-specific mercury Acceptable Daily Intake for use in fish consumption guideline development.

Cardiovascular Endpoints

Many studies have examined the potential association between mercury exposure and cardiovascular health effects. These studies assessed mercury exposure in hair, toenails, and blood and examined endpoints such as blood pressure, heart rate variability, coronary heart disease, stroke, myocardial infarction, and sudden cardiac death. A brief review of select important studies follows (also presented in Appendix Table 2).

The studies that included the largest cohort sizes generally showed no adverse cardiovascular effects associated with mercury exposure. For example, Mozaffarian *et al.* (2011, 2012) evaluated associations between toenail mercury concentration as a marker of exposure and incidence of hypertension, coronary heart disease incidence, and/or stroke incidence in two prospective cohorts, the Health Professionals Follow-up study (51, 529 men) and the Nurses' Health Study (121,700 women). There were 6,045 cases of incident hypertension and 3,427 cases of coronary heart disease and stroke among the cohorts. The authors reported no adverse association between mercury exposure (up to 1.1 pm in toenails) and cardiovascular indices.

Yoshizawa *et al.* (2002) had also analyzed data from the Health Professionals study a decade earlier. They found no association between toenail mercury exposure in the highest quintile of exposure (median hair mercury = 1.34 ppm) and coronary artery surgery, nonfatal myocardial infarction (MI), or fatal and incident coronary heart disease (CHD) as compared to lower exposures. It is important to note that the researchers collected toenails for mercury analysis only at the beginning of the study and therefore actual mercury exposures could have changed in subsequent years when the cardiovascular events occurred.

Xun *et al.* (2012) conducted a meta-analysis of 19 prospective cohort studies that evaluated (via questionnaire) the association between fish consumption and risk of stroke. The meta-analysis cohort from all studies included 402,127 adults (10,568 incident strokes). The authors found *reduced* risk of stroke incidence associated with consuming >5 meals of fish/week as compared to consuming <1 meal/month or no fish. The authors reported that this inverse association was particularly strong in studies based in North America (Xun *et al.*, 2012).

Yorifuji *et al.* (2010) evaluated hypertension risk in 3038 people living in Minamata, Japan and surrounding regions. The authors reported no statistically significant risk of hypertension in association with mercury exposure as high as 28.3 ppm in hair, although the small number of people in each exposure group in this study (approximately 30) may have limited the ability to detect any true associations. This study did not account for several determinants of hypertension, such as sodium intake and physical activity, therefore lending less certainty to the outcomes. The study authors reported a relationship between region and hypertension risk with Minamata, the high exposure region, having the highest risk. However, there was no meaningful exposure-outcome relationship based on this study's outcomes, as the "low" mercury exposure area was associated with higher hypertension risk than "medium" mercury exposure area.

Several smaller studies evaluated the effect of mercury exposure in adults on hypertension. Mordukhovich *et al.* (2012) performed a cross-sectional study that included 639 adult men and women from the Veterans Administration Normative Aging study (median toenail mercury = 0.22 ppm), but found no association between mercury exposure and blood pressure. Virtanen *et al.* (2012a) also found no adverse association between mercury exposure (mean hair mercury = 2 ppm) in 768 Finnish adults and blood pressure outcomes, although they reported reduced pulse pressure and systolic blood pressure associated with the sum of serum omega-3 fatty acids, docosahexaenoic acid, eicosapentaenoic acid, and docosapentaenoic acid (EPA+DPA+DHA). Nielsen *et al.* (2012) found *lowered* diastolic blood pressure (p=0.004) among adult Inuit men in Greenland associated with elevated blood mercury concentrations (highest quintile of exposure = 81 μg/L) *vs*. lower quintiles in this male cohort (mean blood mercury concentration = 20.5 μg/L). This beneficial association may be attributed to concurrent increased intake of omega-3 fatty acids and other nutrients from fish. This association was not observed in women (mean blood mercury concentration = 14.7 μg/L).

Yaginuma-Sakurai *et al.* (2010) performed an intervention study to evaluate cardiovascular outcomes potentially associated with the Japanese mercury Provisional Tolerable Weekly Intake (PTWI) level of 3.4 μg methylmercury/kg body weight/day from fish consumption. The authors recruited 14 men and 13 women in each of the exposed and control groups. The exposed participants had a fish diet aimed to achieve a mercury intake equivalent to the PTWI. The exposed participants had an average hair mercury concentration of 8.76 ppm after 15 weeks on this diet, at which time the participants reverted to their original fish diet. The control participants were maintained at a steady fish intake throughout the study, which was associated with approximately 2.3 ppm average mercury concentration in hair. At the 29th week (end of the study), the exposed group had an average hair mercury concentration of 4.9 ppm. The authors reported elevated heart rate variability (HRV) indicators of sympathetic tone and sympathetic/parasympathetic balance (low frequency domain of HRV, LF, and the ratio of the low frequency to high frequency HRV, LF/HF, respectively) associated with 8.76 ppm average hair mercury as compared to both the 2.30 ppm average baseline and the 4.9 ppm average post exposure/clearance. However, no associations between mercury exposure and coefficient of variation of R-R interval (CVRR), coefficient of variation of the high frequency component of HRV (CVHF), or heart rate were observed. While this study suggests an effect of increased mercury intake on some HRV parameters, these effects may be transient. It is not clear if the reported changes in HRV would have persisted if the diet containing elevated mercury had persisted. Also, approximate doubling of hair Hg at end *vs*. baseline was associated with similar HRV parameters. This suggests that these subjects either acclimatized to the mercury effect on HRV, cleared out the mercury load so that the effect was not comparable as during higher exposure, or the association was due to another unmeasured factor. The clinical significance of these HRV associations with mercury is not clear, particularly when HR in this study and BP in others (Nielsen *et al.* 2012; Virtanen *et al.*, 2012a; Mordukhovich *et al.*, 2012) were not associated with mercury exposure. In addition, several HRV parameters remain unchanged in this study despite the elevated mercury exposure.

A series of cross-sectional studies evaluated HRV outcomes in addition to HR and BP in Inuit Canadians in villages of Nunavik in Arctic Quebec (Valera *et al.*, 2008, 2009, 2012, 2013). The authors reported mixed results of an association between mercury exposure and blood pressure in adults, although they noted elevated HR with elevated Hg exposure. HRV parameters were also variably associated with adult and child (11 y) mercury exposure, although the clinical significance or validity of these findings is uncertain, particularly given the cross-sectional nature of these studies and the lack of adjustment for several potential confounders such as salt intake. Prenatal mercury exposure was not associated with HRV parameters in 11-year-old children.

A limitation in the literature evaluating potential cardiovascular health outcomes of mercury from fish is that most studies do not have concentrations as high as those that examined neurodevelopmental outcomes in the Seychelles, Faroe Islands, and New Zealand studies, and therefore, cardiovascular effects at these high concentrations are not well known. Nonetheless, our survey of the literature indicates that the largest studies in this area show no adverse association between mercury exposure or fish intake with cardiovascular diseases. Alternatively, some of these studies showed beneficial outcomes associated with frequent fish consumption. Smaller, mainly cross-sectional studies with limited accounting for potential confounders, show mixed results with some statistically significant associations reported in some studies, but not in others. The clinical significance and validity of these findings in the smaller studies requires further study and validation.

Diabetes Endpoints

Few studies have examined the potential association between mercury exposure from fish consumption and the risk of developing diabetes. Moon *et al.* (2013) performed a cross-sectional study using NHANES data from Korea and found no association between diabetes and mercury exposure in Korean adults. Xun and He (2012) performed a meta-analysis that included 438,214 subjects (18,711 incident diabetes cases) from 12 prospective cohort studies that evaluated an association between fish consumption and diabetes incidence. The authors found no diabetes risk associated with consuming ≥5 meals of fish per week. However, they found *reduced* diabetes incidence associated with increased fish intake in “Eastern” country cohorts. The authors found no such association in “Western” country cohorts. In contrast, the same authors (He *et al.*, 2013) reported an elevated diabetes incidence risk in a U.S.-based prospective cohort of adults exposed to mercury as measured in toenails. The authors reported elevated risk in those adults within the highest quintile of mercury exposure (median toenail mercury = 0.61 ppm) *vs*. lowest quintile (median toenail mercury = 0.07 ppm). While the association was statistically significant, there is at least one important limitation to this study. For example, the study cohort was followed for 20 years (1985–2005), but mercury exposure was only determined at baseline. Therefore, it is uncertain if the association observed is a true one, as mercury exposure can change with time and is heavily dependent on lifestyle. Interestingly, authors from this same research group (Li *et al.*, 2013) found reduced diabetes incidence in association with increased exposures to long chain omega-3 fatty acids. Likewise, Virtanen *et al.* (2014) found that the risk of Type 2 diabetes decreased with increasing EPA+DPA+DHA intake in a prospective cohort of Finnish men.

Another meta-analysis (Wallin *et al.*, 2012) evaluated data from 16 prospective cohorts (527,441 subjects; 24,082 incident diabetes cases) that examined the association between fish intake and diabetes incidence. The study authors reported mixed results. For example, “Western”-based studies from U.S. showed a marginally significant association between diabetes incidence and increments in fish intake (RR=1.05; 95% CI, 1.02–1.09), but European and “Asian/Australian” studies did not (RR=1.03; 95% CI, 0.96–1.11 and RR=0.98; 95% CI, 0.97–1.00, respectively). Table 3 in the Appendix presents additional details for the studies presented in this section.

Radiation

The nuclear reactor accident in northeast Japan caused by the March 11, 2011 earthquake and tsunami released radioactive material into the Japanese coast and neighboring environments. This has raised some concerns about radiation from Japan impacting Alaska fish.

The U.S. Food and Drug Administration (FDA) routinely measures radiation levels in commercial foods to assure a safe food supply. The FDA is the primary agency conducting routine testing and monitoring of food imported from Japan and other countries before and after the Fukushima nuclear accident. As of March 2014, FDA had tested 1,345 food products imported from Japan, 225 of which contained seafood from Japanese waters; none of the imported products contained radioactive material concentrations that would be associated with risk to public health if consumed.

Testing of seafood for Fukushima-derived radiation by academic institutions, research organizations, some Pacific states, and Canada supports the safety of Pacific seafood. For example, a study by Fisher *et al.* (2013) found no to minimal cancer risk associated with Fukushima-derived radioactive material for someone who would consume a large amount of

Pacific bluefin tuna caught in California coastal waters (these tuna likely foraged very close to the Japanese coast, according to the study authors).

Research tracking Pacific Bluefin Tuna migration patterns have identified that these fish can carry some Fukushima-derived radiation if they move from Japan to California water (Madigan *et al.*, 2012, 2013). However, these studies show that the radiation levels attributed to the Fukushima accident are much lower than the naturally occurring radioactive material such as potassium-40 and polonium-210 present in these fish (Madigan *et al.*, 2012, 2013). Moreover, these studies show that Fukushima-derived radionuclide levels have declined from 2011 to 2012 (Madigan *et al.*, 2012, 2013). The study by Fisher *et al.* (2013) supports the minimal to no health risk associated with consuming large quantities of this tuna on a daily basis.

ADEC and DHSS continue to monitor the Fukushima situation closely. For more information on radiation in Alaska fish, other seafood, air, and water, please see the ADEC (ADEC, 2014) and DHSS (DHSS, 2014b) radiation websites.

Developing an Acceptable Daily Intake for Fish

There is currently no consensus on methylmercury dietary exposure guidelines from fish. For example, FDA, the U.S. Agency for Toxic Substances and Disease Registry (ATSDR), and EPA each use different epidemiological studies, methods, and calculations to derive distinct guidelines (Table 7). FDA bases their dietary intake guidelines for methylmercury on knowledge gained from the acute poisoning episodes in Minamata and Niigata, Japan and Iraq. ATSDR bases their intake guidelines on the Seychelles data, while EPA uses Faroe Islands data, and WHO considers both studies in addition to the New Zealand study. In following with our determination to use the Seychelles study for risk assessment purposes, we chose to use results from a benchmark dose modeling approach instead of a more traditional No/Lowest Observed Adverse Effect Level (NOAEL/LOAEL) approach. A description of our approach follows.

Crump (1984) defined the benchmark dose (BMD) as a lower 95% confidence limit on the dose corresponding to a moderate increase (*e.g.*, 1% to 10%) in effects from exposure over the background rate of exposure and effects. This percent increase is used because it is usually in the range of the sensitivity of the study or assay being used to extract the BMD. Crump and others have argued that its estimation is relatively robust to model choice. The BMD modeling approach fits a regression model characterizing the mean of the outcome of interest as a function of dose and assumes that the data are normally distributed. Using the fitted model, one then calculates the dose-specific probability of falling into the abnormal region. The BMD is estimated as the dose corresponding to a specified increase in that probability, compared with the background probability. The BMDL is the corresponding 95% lower limit on that dose.

When exposure measures are continuous, such as in the studies conducted in the Seychelles Islands, Faroe Islands, and New Zealand to evaluate neurodevelopmental outcomes associated with fish consumption and mercury, there is no apparent threshold dose above which adverse effects start to occur. Therefore, in such cases, benchmark dose modeling is a reasonable choice in determining an acceptable daily intake in contrast to the NOAEL/LOAEL approach that leaves much uncertainty in its outcome. In fact, studies that compared BMD and NOAEL methodologies found that the NOAEL either underestimated or overestimated the BMD (Allen *et al.*, 1994; Kimmel *et al.*, 1995; Sand *et al.*, 2008).

Seychelles Islands

The data from the testing of the 107-month (Myers *et al.*, 2003) was used in a benchmark dose analysis performed by van Wijngaarden *et al.* (2006). The average 95% lower confidence limit of the BMD (BMDL) across all 26 neurobehavioral endpoints evaluated in the study varied slightly among the three models used (k-power, Weibull, and logistic). The choice of statistical model did not significantly affect the BMDL estimates. The lowest BMDL of 20.1 ppm (range: 17.2 – 22.5) was calculated using the logistic model, while the highest BMDL calculated, 20.4 ppm (range: 17.9–23.0) was determined using the k-power model. The lowest BMDLs reported in this study were 17.2 ppm for the logistic model with the benchmark response (BMR) set at 10% and 15.5 ppm for the k-power model with the BMR set at 5%. The study authors recommend presenting an average BMDL and its corresponding range based on all available evidence to provide an indication of the exposure limits within which the true BMDL is likely to fall. BMDLs based on hair mercury concentrations in this cohort are presented in Table 4.

Faroe Islands

The adverse associations observed in the Faroe Islands study were most sensitively detected when using cord blood as the biomarker. Based on cord-blood analyses, the lowest reliable BMD was reported for the Boston Naming Test (BMDL for reaction time was lower, but a large amount of data were discarded for this test, therefore adding uncertainty; NRC, 2000). This BMDL of 58 ppb represents the lower 95% confidence limit on the dose that is estimated to result in a 5% increase in the incidence of abnormal scores on the Boston Naming Test (Budtz-Jorgensen *et al.*, 1999; NRC, 2000). The Faroe Islands study researchers reassessed this analysis and recommended that based on uncertainties in exposure assessment, the actual mercury exposure associated with adverse health outcomes is lower (Budtz-Jorgensen *et al.*, 2004). However, this reanalysis requires further examination, as it indicates a large difference from the hair mercury association with performance on the Boston Naming Test in this cohort (Budtz-Jorgensen *et al.*, 2000). BMDLs based on cord blood and hair mercury concentrations in this cohort are presented in Table 4.

New Zealand

Crump *et al.* (1998) used New Zealand cohort study data to calculate BMDs and BMDLs associated with a 10% response rate in study test performance. BMDs (10% response rate) calculated from five neurodevelopmental tests ranged from 32 to 73 ppm. This corresponded to a benchmark dose level (BMDL10) range of 17 to 24 ppm. This calculation was based on data that included, in the high mercury exposure group, a child whose mother had a hair mercury level of 86 ppm, which was more than four times higher than the next highest hair mercury level of 20 ppm. Although none of the test scores of this child were outliers according to the definition used in the analyses, his scores were significantly influential in the analyses. When this child was omitted from the analyses, BMD10s ranged from 13 to 21, with corresponding BMDLs of 7.4 to 10 ppm. BMDLs based on hair mercury concentrations in this cohort are presented in Table 4.

The National Research Council (NRC, 2000) used data from this study to derive a BMDL5 that ranged from 4 ppm to 6 ppm hair mercury for the different neurodevelopmental test results from this cohort.

Table 4. Benchmark Dose Outcomes of Hair Mercury Concentrations (ppm) for the Three Main Studies on Neurodevelopmental Outcomes and Mercury in Fish

Cohort	Study/Analysis	Main Dietary Source of Mercury	BMDL10*	BMDL5*
Seychelles Islands	Wijngaarden *et al.* 2006	Fish	17.9, 18.0, 23.0	15.5, 16.1, 21.9
Faroe Islands	Budtz Jorgensen *et al.*,2000	Fish and Marine Mammals (Pilot Whale)	16, 16, 22 **	9.4, 9.6, 13.4 **
New Zealand	Crump (1998); NRC (2000)	Shark and other fish	7.4, 9.5, 10 (Crump, 1998)	4, 6, 6 (NRC, 2000)

**Most sensitive, second most sensitive, and least sensitive endpoint-associated Benchmark Dose Lower statistical Bound (BMDL)*
***Corresponding values based on blood mercury concentrations are 76, 96, 132 ppb (BMDL10) and 46, 58, 79 ppb (BMDL5) (Budtz-Jorgensen et al., 2000)*

Acceptable Daily Intake

To derive a point of departure for derivation of an acceptable daily intake of mercury in fish, we selected the hair mercury concentration associated with the lowest BMD associated with a test result in the Seychelles cohort (time to complete the Grooved Pegboard task). We also selected the BMD produced from the most conservative model derived for that endpoint at BMDL05. We then used the following equation and parameters used by ATSDR (1999) to calculate the acceptable daily intake (d):

$$d = \frac{C.b.V}{A.f.BW}$$

where

d = dietary intake (µg methylmercury per day)
C = concentration in blood (µg/L) (ppm concentration in hair divided by 250)
b = elimination constant ($days^{-1}$) (0.014)
V = volume of blood (L) (4.2)
A = absorption fraction (unitless) (0.95)
f = fraction of absorbed dose taken up by blood (unitless) (0.05)
BW = body weight (kg) (60 kg – women of childbearing age)

We accounted for interindividual differences in mercury elimination by applying a factor of 2.3 to account for pharmacokinetic variability among people. This variability factor represents the average of variability in the relationship between the concentration of mercury in maternal hair and the ingested dose of methylmercury predicted by analyses from Stern (1997) and Clewell *et al.* (1999) (as summarized in by the National Academy of Sciences Committee on the Toxicological Effects of Methylmercury; NRC, 2000). This factor represents the average of the ratios of 50^{th} percentile:1^{st} percentile of ingested methylmercury in hair. This ratio of dose estimates is inclusive of the variability in 99% of the population and suggests that the pharmacokinetic variability in the population is highly unlikely to be larger than a factor of 2.3. A comparison of maternal blood methylmercury to ingested mercury dose yields the same factor, 2.3 (as summarized in NRC, 2000). This factor is similar to that used by ATSDR (factor = 3) in developing the MRL for mercury (ATSDR, 1999).

The aforementioned methodology produced a daily acceptable intake equivalent to 0.56 µg methylmercury/kg body weight/day for women of childbearing age.

Federal and International Criteria for Acceptable Mercury Exposure Levels in Humans

World Health Organization (WHO)

The WHO recently used a quantitative risk-benefit approach to develop an acceptable daily intake of fish that is dependent on both the mercury concentration in fish and the sum of long chain omega-3 fatty acids (EPA and DHA) concentration in fish. This approach was designed to protect against what the WHO committee considered the most sensitive health outcomes of mercury exposure, the neurodevelopmental effects in the children of mothers who may consume fish. In general, fish low in mercury and high in omega-3 fatty acids were recommended in larger quantities than those high in mercury and low in omega-3 fatty acids. To develop an acceptable fish intake based on mercury content, the report authors used a central estimate of Intelligence Quotient (IQ) decrement = -0.18 IQ points associated with an increase of 1 ppm mercury in maternal hair derived from an analysis of Faroe Islands, Seychelles Islands, and New Zealand studies (Axelrad *et al.*, 2007). The report authors also used an upper-bound estimate = -0.7 IQ points per 1 ppm increase in maternal hair mercury concentrations derived from Faroe Island data (Cohen, Bellinger, and Shaywitz, 2005). Long chain omega-3 fatty acid benefits on IQ were estimated as 4.0 IQ points gained per daily maternal ingestion of DHA based on the outcomes of the ALSPAC study and Project Viva (FAO/WHO, 2011). The WHO recommendations can be translated to derive an acceptable daily dose of mercury in fish ≥0.8 µg methylmercury/kg body weight/day.

Prior to this assessment, the WHO established a Provisional Tolerable Daily Intake of 0.5 µg/kg body weight per day for adults other than women of childbearing age, which the WHO reaffirmed in 1999 (JECFA, 2000). This Provisional Tolerable Daily Intake for the "general population" was established for adults from the Japanese data, and is based on a Lowest Observable Adverse Effect Level for methylmercury in whole blood of 220 ppb (52 ppm hair). WHO used an uncertainty factor of 10 to derive the Provisional Tolerable Daily Intake. Similarly, the Iraqi data provided a Lowest Observable Adverse Effect Level of 240 ppb to 480 ppb in whole blood. For adults the clinical adverse effect detectable at the lowest methylmercury dose is paresthesia (a numbness and tingling sensation) of the mouth, lips, fingers, and toes. The Japanese hair samples were originally analyzed by the dithizone procedure, yielding a value of 52 ppm in the patient with paresthesia with the lowest level of hair mercury. A later reanalysis of the hair from that patient using the newer atomic absorption technique yielded a value of 82.6 ppm (WHO, 1990). All other affected individuals had hair levels above 100 ppm.

Based on available models, a consistent intake of the WHO's Provisional Tolerable Daily Intake (0.5 µg/kg/day) would correspond to a blood concentration of 20 ppb and a hair mercury concentration of 5 ppm. These exposure levels are one tenth of the Lowest Observable Adverse Effect Level of 220 ppb (blood) in the Japanese data.

The 1999 WHO Committee also noted "that fish (the major source of methylmercury in the diet) contribute importantly to nutrition, especially in certain regional and ethnic diets, and recommended that, when limits on the methylmercury concentration in fish or on fish consumption are under consideration, the nutritional benefits are weighed against the possibility of harm." (JECFA, 2000)

U.S. Food and Drug Administration (FDA)

FDA derived its action level for commercial sale of 1 ppm mercury (wet weight) in the edible portion of fish based on the Japanese data (Friberg, 1971). FDA calculated the action level for edible portions of seafood for interstate commerce by assuming an acceptable methylmercury daily intake of 0.5 µg per kg body weight per day, a half pound (226 g) of fish consumed per week, and a 70 kg adult, resulting in a tolerance level of 1 ppm (1 ppm = [0.5 µg/kg x 7 days x 70 kg]/226 g of seafood consumption). FDA recently reaffirmed its position on the guideline in response to a request to consider lowering this action level (FDA, 2013).

U.S. Agency for Toxic Substances and Disease Registry (ATSDR)

ATSDR derived an oral Minimal Risk Level of 0.3 µg per kg body weight per day (ATSDR, 1999) based on the 66-month evaluation of the Seychelles Child Development Study (Davidson *et al.*, 1998). ATSDR selected the mean maternal hair level of 15.3 ppm in the group with the highest exposure to represent the No Observed Adverse Effect Level and derivation of the chronic oral Minimal Risk Level for methylmercury. An uncertainty factor of 4.5 was used to account for human pharmacokinetic and pharmacodynamic variability (3.0) and the lack of domain-specific tests (1.5) that tested positive in the Faroe Island cohort, but had not been conducted in the Seychelles..

ATSDR stated that the modifying factor of 1.5 could be removed if the results of the domain-specific tests in the 96-month Seychelles evaluation are consistent with previous results (*i.e.*, no effects due to methylmercury exposure). As noted earlier, preliminary results of the 107-month evaluation do not support an association between prenatal exposure to low levels of methylmercury from consumption of ocean fish with background levels of contamination and adverse neurodevelopmental consequences.

ATSDR recently published an addendum (ATSDR, 2013) to its mercury toxicology profile (ATSDR, 1999) that provided a review of selected epidemiology and toxicology studies published since 1999.

U.S. Environmental Protection Agency (EPA)

In 2001, EPA adopted the reference dose of 0.1 µg/kg body weight/day for methylmercury developed by the National Academy of Sciences (NRC, 2000) by using the results of the Faroe Islands study (Grandjean *et al.*, 1997, 1998). Grandjean *et al.* (1997) reported "significant associations between either maternal hair mercury or cord-blood mercury and decrements in several neuropsychological measures." The NRC selected the Boston Naming Test, the test associated with the second most sensitive endpoint in the study, as the critical endpoint. To estimate the level of exposure or dose that is associated with an increase in adverse effects, or "benchmark dose", the NRC relied on the statistical analysis performed by Budtz-Jorgensen *et al* (1999). The benchmark dose, defined as the dose associated with a doubling of the rate of incorrect responses on the Boston Naming Test (from 5% to 10%), was 85 ppb mercury in cord blood. Using current models and applying an uncertainty factor of 10, the NRC then used the lower 95% confidence limit of the benchmark dose (associated with the 5% benchmark response), *i.e.*, 58 ppb, to calculate a reference dose of 0.1 µg/kg body weight/day (Marsh *et al.*, 1987). The reference dose of 0.1 µg/kg/day corresponds to a hair concentration of approximately 1.2 ppm and a blood concentration of 5.8 ppb.

Health Canada

Health Canada has derived a provisional tolerable daily intake (PTDI) for women of reproductive age and infants of 0.2 µg/kg body weight/day, and they use 0.5 µg/kg body weight/day for other adults (NRC, 2000). Based on the recent epidemiological data, Health Canada established a provisional No Observable Adverse Effect Level of 10 ppm mercury in maternal hair. By applying an uncertainty factor of 5 to account for interindividual variability, Health Canada derived the Provisional Tolerable Daily Intake of 0.2 µg/kg body weight/day (NRC, 2000). For biomonitoring studies, Health Canada applies the following ranges: a blood mercury value of ≤ 20 ppb is normal, 20 ppb to 100 ppb is the level of concern, and greater than 100 ppb is their action level (van Oostdam *et al.*, 2003; AMAP, 2003). A blood value of 20 ppb corresponds to approximately 5 ppm in hair.

Table 5. Guidelines for Women of Childbearing Age Derived by Various Agencies for Mercury

Agency	Point of Departure	Primary Study/Studies	Acceptable Daily Intake Level (µg/kg BW/day)	Safety Factor
JECFA (FAO/WHO)	Not Applicable (Risk Benefit Calculation)	Seychelles Islands; Faroe Islands; New Zealand	>0.8 µg/kg/d	None. Upper risk estimate
ATSDR	15.3 ppm in maternal hair NOAEL	Seychelles Islands	0.3 µg/kg/d	4.5
Alaska 2007	15.3 ppm in maternal hair NOAEL	Seychelles Islands	0.4 µg/kg/d	3
US EPA	58 ppb in maternal blood LOAEL	Faroe Islands	0.1 µg/kg/d	10
Health Canada	10 ppm in maternal hair NOAEL	Literature Review*	0.2 µg/kg bw/day	5
US FDA	200 ppb in blood LOAEL	Japan	0.5 µg/kg/d	10

* Feeley, M.M. and Lo, M.-T. Risk Assessment for Mercury in Health Canada - Development of the Provisional Tolerable Daily Intake (pTDI) Value. In: Proceedings of the Conference on Mercury in Eastern Canada and the Northeast States, 21–23 September, 1998. Ed. by Pilgrim, W., Burgess, N., Giguère, M.-F. 1998. Unpublished.

Arctic Monitoring and Assessment Programme (AMAP)

Since 1991, the international Arctic Monitoring and Assessment Programme (AMAP) has evaluated the potential human health impacts of exposures to arctic contaminants such as mercury and PCBs (AMAP, 2002, 2003). Public health officials from AMAP and other arctic scientists have concluded that the nutritional and physiological health benefits of traditional arctic subsistence foods outweigh potential risks in most areas of the Arctic, and advise local public health policy makers to encourage continued traditional food use when indicated by risk-benefit analyses (AMAP, 2002, 2003).

This was highlighted at the 2002 AMAP meeting in Rovenemi, Finland by the AMAP human health working group, and at the 2002 Arctic Council meeting in Saariselka Finland. They also stated that public health officials should use methylmercury intake guidelines only as tools to craft dietary advice, not as a strict standard. The AMAP noted that the EPA reference dose for methylmercury only considers the potential risks and does not take into account the well-known benefits of fish consumption.

Local Risk Management Issues for Mercury in Fish from Alaska

It is widely recognized that local risk management is an essential element of developing optimal public health advice regarding consumption of locally-caught fish (EPA, 1996; IOM, 2007). States vary tremendously in many relevant ways, including reliance on locally caught fish, consumption practices, contaminant concentrations in local fish, and the health status of local populations. When only weak data support an association between an exposure and adverse outcomes, as is the case for mercury exposure at the levels present in most Alaska fish, then public health officials can place more weight on factors such as local economics and cultural considerations when developing consumption advice.

Alaska has many unique characteristics that distinguish it from the rest of the nation (and that distinguish individual regions within Alaska from each other). These include the vast geographical distances and limited transportation systems that limit alternate food choices in rural villages, a heavy reliance on fish as a subsistence food, both for basic caloric needs and nutrition and as an anchor for Native culture, and an abundant supply of fish with extremely low mercury levels.

Description of Alaska

Alaska, encompassing 586,412 square miles, is larger than Texas, California, and Montana combined. To walk across this “great land” at its widest point would be to walk from California to Florida: 2,400 miles from west to east and 1,420 miles from north to south.

The 2012 Census estimated the population of Alaska as 730,307 people. Of these, 68% were white. Alaska Native people comprised 15% of the population. Within the Alaska Native population are the following groups: Aleut, Eskimo (Yupik, Inupiat), and Indian (Athabaskan, Tlingit, Haida, and Tsimshian). Based on 2012 estimates, 42% of the State’s population resided in Anchorage, 52% in the three largest cities (Anchorage, Fairbanks, and Juneau), and 77% in the five largest census areas (Anchorage, Fairbanks, the Kenai Peninsula, Matanuska-Susitna Borough, and Juneau). While white people constituted approximately 70% of all Alaskans living in Alaska’s largest cities, Alaska Natives and American Indians constituted only 9%. Alaska Natives are the main inhabitants of rural towns and villages with less than 1,000 people.

Only five of Alaska’s urban centers are connected by road. Alaska includes vast wilderness areas dotted with isolated villages, some with fewer than a dozen people. Many villages lack basic public health infrastructure such as in-home piped water and septic systems (Goldsmith *et al.*, 2004), and remain accessible only by small airplane or boat. Throughout rural Alaska, local economies are poorly developed and many residents live below the federal poverty line. Most villagers in rural Alaska rely on the land and its wildlife as a major food source; subsistence food gathering includes hunting, fishing, trapping, and gathering wild berries and other plant products.

Cultural and Societal Importance of Fish in Alaska

The use of traditional foods, including fish, provides a basis for cultural, spiritual, health, nutritional, medicinal, and economic well-being among Alaska Native people and indigenous peoples. The social aspects of sharing in subsistence harvests and feasts associated with age-old traditions are integral to the cultural fabric of current-day Alaska Native people. Subsistence activities use local knowledge and skills and provide an opportunity to pass on knowledge from generation to generation, preserving cultural and community identity. Subsistence harvest activities are an opportunity for physical activity, self-reliance and meaningful productive work, especially in remote areas where few wage paying jobs exist. Thus, traditional food is "the basis of social activity and of the maintenance of social bonds through its production and distribution. This is the essence of subsistence not simply as an activity, but as a socio-economic system (Usher *et al.*, 1995)." A social study that surveyed the Inuit communities in northwest Alaska found that subsistence participation fostered community ties and social support which significantly impacted life satisfaction (Martin, 2012). Thus, the social and cultural disruption associated with food consumption advisories can have profound and measurable effects on the health and well-being of subsistence communities (Wheatley, 1994). One Alaska Native leader put it this way: "The act and ritual of our subsistence food activities encompass who we are, and all that we are and is a vital source of our spirituality. I emphasize these things because I want you to know how much of an impact the threat of contaminants has on these things which are so sacred to us." (Sally Smith, Chair, Alaska Native Health Board).

The importance of fish and the act of fishing extends beyond Alaska Native people to influence the majority of all Alaskans. In 2007, approximately 476,000 anglers were licensed for recreational fishing in Alaska; nearly 40% of those anglers were Alaska residents (Southwick Associates, 2008). Anglers fished 2.5 million days in Alaska and spent nearly 1.4 billion dollars on licenses, stamps, equipment, real estate, and other trip-related expenditures (Southwick Associates, 2008). The primary motivation for many of these fishers was to obtain fish for food. Alaska's Personal Use fisheries are designed to allow Alaskan residents to harvest fish for food in designated areas that are not eligible for subsistence fisheries (such as Cook Inlet) using fishery-specific techniques, such as dipnetting or gillnetting (ADF&G, 2007). Many urban (and other) Alaskan families have embraced this unique opportunity to harvest sufficient salmon (or other species in some areas) to eat throughout the year.

Economic Importance of Subsistence

In addition to the socio-cultural value and associated physical activity, traditional foods such as fish have great economic value in Alaska. In rural Alaska, family incomes are often low and locally-bought store-bought foods are several times the price found in Anchorage, so traditional foods such as fish provide an important source of nutritious food in many communities. Approximately 90% of rural households participate in subsistence activities, as traditional foods can be obtained with little or moderate costs compared to the cost of market foods.

Unemployment is relatively high in rural Alaska, although published figures typically underestimate unemployment rates (Goldsmith *et al.*, 2004). During 2005–2007, the unemployment rate among Alaska Natives averaged 21%; this was 3 times higher than the national average during this period (Martin and Hill, 2009). Only about 25% of employed Alaska Native people hold jobs in remote rural areas outside of the regional centers (Goldsmith *et al.*, 2004). During 2005–2007, 22% of Alaska Native people lived in households with incomes below the national poverty level (Martin and Hill, 2009), and during 2000, the per capita income in remote areas was $14,032 (Goldsmith *et al.*, 2004). These statistics mask worse economic conditions in some villages, generally those with a high reliance on subsistence food gathering.

Despite low economic status, the geographic isolation, high transportation costs, and harsh climate in rural areas of Alaska contribute to a much higher cost of living compared to urban areas. Electricity can cost four times more in rural Alaska, and food generally costs at least 50% more (Goldsmith *et al.*, 2004). Store-bought foods are very expensive in rural Alaska, particularly in remote areas inaccessible by road where food items must be imported by plane or boat. For example, food for a week for a family of four eating at home costs $337 in Bethel, $173 in Nome, and $165 in Anchorage according to a recent survey (UAF, 2013).

Statewide, the costs associated with replacing subsistence foods with market substitutes in rural Alaska ranges from $134–$268 million annually (ADFG, 2010). In Arctic Alaska, where residents harvest an average of 436 pounds of wild foods per person annually, the cost of replacing those foods with market foods (assuming a $3.5–$7/pound replacement value) would total $1527– $3055 per person per year (ADFG, 2010); in Western Alaska, the range would be from $39–$79 million annually. Recent analyses of subsistence data from ADF&G performed by the Alaska Department of Community and Economic Development estimates that subsistence harvests provide residents of the Arctic Alaska with 42% of their caloric requirements, and nearly four times the amount of protein consumed by the typical American (ADFG, 2010). Thus, replacing subsistence foods with market foods presents both negative health and economic consequences to Alaska Native people and other rural Alaska residents.

Recreationally-caught fish are also valued economic assets to Alaskans. Alaskan participants in recreational fishing expect to receive benefits of greater value than the expenses they incur when going fishing. Economists estimate that the “net economic value” (the value over and above expenses) that those who sport fish in Alaska place on their annual recreational fishing is $186 million (in 1993 dollars; Haley *et al.* 1999).

Employment Significance of Alaska Fisheries

The commercial fishing industry in Alaska provides many Alaska residents with a livelihood. Alaska's commercial fishing industry is the number one private basic sector employer in Alaska, providing more jobs than oil, gas, timber, or tourism (ADCCED, 2007). The Southeast region has the largest fish harvesting workforce in Alaska. In 2010, the commercial fishing industry in Southeast Alaska alone employed 9,182 Alaska residents (ADOL, 2011). Thriving commercial fishing industries provide employment to many Alaska residents in other parts of the state, including Dutch Harbor, Kodiak, Naknek-King Salmon, Seward, Homer, Kenai, Bristol Bay, and the Aleutian/Pribilof Islands. In 2010, over 4.35 billion pounds of seafood was harvested from Alaska waters, worth $1.6 billion and accounting for 53% of the entire U.S. seafood harvest (ADOL, 2011).

Many Alaskans make a living as sportfishing guides. More than 23% of total angler days fished in 2007 were led by sportfishing guides (Southwick Associates, 2008). In 2006, ADF&G's database included 1,420 sportfishing service businesses (Southwick Associates, 2008). The charter boat industry operates predominantly in Southeast and Southcentral Alaska. As stated by Kevin C. Duffy, former Commissioner of the ADF&G, "Alaska is a world class destination for sport fishing. Alaska's sport fishing guide industry provides access to fishery resources for those who might not otherwise be able to access them. This industry provides significant economic benefits to Alaskans by creating jobs and bringing tourism dollars into Alaska's communities." (ADF&G, 2004, 2007)

Risks of Less Healthful Replacement Foods

In rural Alaska, supermarkets are rare and existing small village stores are often poorly stocked. Residents cannot obtain many fresh foods at any cost. Small village stores sell convenience items including chips, canned soda, and candy, have a limited supply of meat and dairy products, and usually have a poor supply of fresh fruits and vegetables. Thus, an insufficient variety in products exists to provide healthy alternatives to traditional foods, and shopping excursions to major cities and shipping can be costly. The market foods available to replace locally harvested wildlife have higher concentrations of saturated fat, trans-fat, salt, vegetable oils, and carbohydrates and often provide less nutrient value (Receveur *et al.*, 1997).

Dietary shifts away from traditional food use have been documented in some parts of the Arctic. In Canada, approximately 60%–70% of the total energy in the contemporary diet of Dene and Inuit peoples consists of market foods, resulting in a diet much higher in fat and carbohydrates, and lower in protein than their traditional diet (Kuhnlein *et al.*, 2001). Similarly, during a dietary survey of 74 Alaska Native women residing in and near Anchorage, only a small proportion reported eating any traditional foods, and intake was very infrequent. The participants reported high intakes of fats/oils and sweets, and intake of some nutrients was low (Nobmann and Lanier, 2001). While dietary changes are complex in nature, they often coincide with a number of other lifestyle changes that also contribute to increases in chronic diseases such as heart disease, diabetes, and cancer.

Diet and lifestyle factors influence most of the leading causes of death in Alaska. Switching from a subsistence lifestyle and diet to a more sedentary existence and a "Westernized" diet high in saturated and trans fats and carbohydrates has contributed to a pattern of increasing obesity and chronic disease among many indigenous populations in North America and the Pacific Rim (Risica *et al.*, 2000a). The prevalence of obesity in Alaska has increased dramatically in recent years: from 49% in 1991 to 65% in 2011 (DHSS, 2014a), representing a 33% increase. Increasing non-traditional food use and sedentary lifestyles among Alaska Native people have been associated with an increasing chronic disease prevalence, including an increase in hypertension, glucose intolerance, and diabetes (Murphy *et al.*, 1997; Risica *et al.*, 2000a,b).

Health Benefits of Fish Consumption

Fish provide a diet rich in high-quality protein, low in saturated and trans fats, and rich in omega-3 polyunsaturated fatty acids. Fish contains all of the essential amino acids, and is an excellent source of the fat-soluble vitamins A and D, as well as selenium and iodine. Selenium is an essential trace mineral important for the proper functioning of some antioxidant enzymes, the immune system and thyroid gland, and is protective against the toxic effects of mercury (Dorea, 2003).

The traditional Alaska Native diet, which is low in saturated fat and high in monounsaturated fat and omega-3 polyunsaturated fatty acids from fish and marine oils, is considered to be more healthful than the typical Western diet. Fish and marine mammals, and to a lesser extent shellfish, are the only significant direct dietary source of omega-3 polyunsaturated fatty acids (e.g., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)).

In addition to providing omega-3 polyunsaturated fatty acids to the diet, fish is also an excellent source of protein and contains other nutrients in varying quantities, depending upon the species. A 3-ounce serving of cooked king salmon provides 40% of the daily requirement of protein, 9% of the daily requirement for iron, and 7% of the daily requirement for vitamin A (Jensen and Nobmann, 1994).

A dietary shift from fish, marine mammals, wild game meats, and plants to a typical Western diet rich in saturated fat from dairy and meat products and linoleic acid from vegetable oils changes the balance between omega-6 and omega-3 polyunsaturated fatty acids. Specifically, significant dietary increases in omega-6 vegetable oils and decreases in the dietary intake of DHA and EPA (oils from fish and marine mammals) results in an increased ratio of omega-6 to omega-3 polyunsaturated fatty acids in the diet. Diets relying upon fish, wild game and plants provide an estimated 1:1 omega-6 to omega-3 polyunsaturated fatty acid ratio, while the current Western diet provides a ratio that may be as high as 10:1 to 20–25:1 (Simonopoulos, 1991). A high omega-6 to omega-3 ratio enhances ischemic and inflammatory processes, leading to an increase in chronic diseases (Uauy et al., 2000). Eicosanoids derived from omega-6 polyunsaturated fatty acids promote inflammation, while those derived from omega-3 polyunsaturated fatty acids are anti-inflammatory and act as competitive inhibitors of the omega-6 derived inflammatory mediators.

Overall, the health status of Alaska's population has improved greatly during the last fifty years, especially among Alaska Native people. Life expectancy has increased, and infant mortality has decreased. The improvements in health status are associated with public health interventions, including improvements in sanitation, treatment of infectious diseases, prevention efforts such as immunizations, and improved medical care. While 50 years ago infectious diseases were a leading cause of death, today the leading causes of death in Alaska are related to a "Westernized" diet and lifestyle, which has led to increases in cancer, heart disease, and diabetes. Many researchers have recommended maintaining or increasing consumption of foods rich in omega-3 polyunsaturated fatty acids, such as fish, both for the cardiovascular disease prevention benefits, as well as the benefits of preventing other chronic diseases (Dewailly *et al.*, 2002).

Harvest and consumption of fish in Alaska provide important cultural, economic, nutritional, and health benefits. Scientific evidence provides extensive documentation of the nutritional superiority and health benefits of fish relative to many other protein sources. Strong evidence exists that decreased consumption of fish—rather than increased consumption—leads to adverse neurological outcomes in the fetus and young child. Particularly in rural Alaska, where healthful alternatives may be limited, recommendations to restrict fish consumption could result in unintended and undesirable consequences in the population. Reduced reliance on fish and other traditional foods often results in increased consumption of market foods high in carbohydrates, sugars, and saturated fats that provide inferior nutrient value.

Unfortunately, these dietary changes already appear to have affected Alaskans. Increasing use of store-bought, processed foods high in saturated fats, processed sugars, trans-fats, and salt in combination with a sedentary lifestyle contribute to increased chronic disease prevalence rates among Alaska Native people. Dietary changes such as these promote hypertension, glucose intolerance, obesity, diabetes, cardiovascular disease, preterm birth, and cancer.

Scientific research continues to document the many benefits of omega-3 polyunsaturated fatty acids, which are found in high levels in fish (IOM, 2007). These benefits may include a reduced risk of developing cardiovascular disease, diabetes, and cancer. In addition, omega-3 polyunsaturated fatty acids are critical for a healthy pregnancy and neonatal growth and development. Increasing omega-3 polyunsaturated fatty acid consumption could decrease chronic disease prevalence and increase healthy life-years. In Alaska, multiple data sources support the assertion that the benefits of fish consumption far outweigh the small, theoretical risks associated with low-level mercury exposure.

Consensus Recommendations from the Alaska Scientific Advisory Committee for Fish Consumption

After careful evaluation of the information presented thus far, the Alaska Scientific Advisory Committee for Fish Consumption achieved consensus on the following points:

- Fish consumption guidelines for women of childbearing age and children are warranted for a small number of Alaska fish species due to measured mercury levels in these fish (see **Fish Consumption Guidance** below).
- The Seychelles Islands study provides the most appropriate data for determining the human health risks posed by mercury exposure from fish consumption in Alaska. The Seychelles Islander and Alaskan exposure scenarios are comparable, as both populations eat large quantities of ocean fish that have similar mercury as well as lower POP levels than in the Faroe Island fish and pilot whale. Therefore, the Seychelles Islands study provides the most appropriate context and data to develop an Alaska-specific Acceptable Daily Intake for methylmercury for use in consumption guideline calculations.
- The Alaska-specific chronic oral Acceptable Daily Intake for methylmercury for women of childbearing age and children is **0.56 μg/kg body weight/day**. This value was derived using the daily mercury intake in fish associated with the BMDL5 of 15.5 ppm mercury in hair based on the Seychelles Island data, divided by a 2.3-fold uncertainty factor for human pharmacokinetic and pharmacodynamic variability.
- Alaska demographic groups other than women of childbearing age and children may continue to enjoy unrestricted consumption of all fish (except salmon shark) from Alaska waters. Salmon shark should be consumed in moderation due to its relatively high content not only of mercury, but also of PCBs and other POPs.
- Fish consumption advice must be tailored and targeted for specific demographic groups and actual fish species consumed. DPH will develop separate, specific health education materials for the general public eating store-bought fish, subsistence consumers, recreational fishermen, and health care providers.
- People limiting consumption of a particular fish due to mercury concerns may substitute it with an Alaska fish lower in mercury (such as salmon), or with another food of comparable nutritional quality.
- Coordinated and strategic monitoring of both fish and humans should be expanded to fill important data gaps. The process of data evaluation and development of consumption guidance will be an ongoing effort, with updated guidance provided as needed.
- Recreational fishermen and fisherwomen who catch longnose skate, yelloweye rockfish, spiny dogfish, large halibut (≥80 pounds) , large lingcod (≥40 inches), and salmon shark are highly encouraged to contact the ADEC fish monitoring program for testing as these fish can vary considerably in their mercury content and may not be equally suitable for consumption by pregnant women and children.

Acceptable Daily Intakes for Contaminants Vary According to their Purpose: Public Health Practice *vs*. Regulation

Some confusion may result from varying safety guidelines developed by numerous government agencies. In this case, the chronic oral Acceptable Daily Intake for methylmercury for women of childbearing age and children adopted by the State of Alaska for fish consumption advice is 0.56 µg/kg body weight/day. This is approximately 5 times higher than the EPA's Reference Dose of 0.1 µg/kg body weight/day.

The differences in the two agency's guidelines are based on the different purposes for which they were derived. Even though the ultimate goal of both agencies is to protect public health, they each approach that goal from different perspectives, entailing different basic responsibilities.

The EPA is a regulatory agency charged with protecting the environment from pollutant-caused degradation. This agency must establish "acceptable" levels of pollution, and then manage and enforce their decisions through the issuance of waste discharge permits, punitive actions on violators, and other regulatory mechanisms. These acceptable levels of pollution must be scientifically defensible and based on potential harm to pollutant receptors, such as humans or endangered species. Since the EPA is responsible for controlling the input of pollutants into the environment, it is important for that agency to be conservative, and incorporate adequate safety factors to err on the side of caution. EPA's over-riding goal is to minimize risk.

In recognition of the importance of fish consumption for optimal health, the latest advisory from the EPA and FDA (available for comment; Federal Register 79 FR 33559, Docket No. FDA-2014-N-0595) recommends an optimal amount of fish consumption of 8 ounces to 12 ounces for sensitive populations, as opposed to a restrictive upper limit of 12 ounces, to encourage consumption of nutritious fish among pregnant women and other women of childbearing age.

In contrast, as public health agencies grapple with the issue of fish consumption advice, public health officials must balance the risks of contaminant exposure against the known benefits of fish consumption. In this task, they must react to environmental pollution that has already occurred, by developing the most appropriate consumption guidance, given the circumstances faced in their respective jurisdictions.

In developing fish consumption advice, public health officials maximize public health by finding a balance between two opposing actions that each carry a risk of harm. If the public is encouraged to eat fish, they encounter potential health risks associated with exposure to contaminants. If the public is encouraged not to eat fish, they encounter potential health risks associated with replacement foods that may be of inferior nutritional quality, and the loss of health benefits associated with fish consumption. In this case, Alaska public health officials have reached a balance by that aims to protect Alaskan fish consumers from being exposed to potentially harmful levels of mercury.

DPH asserts that the chronic oral Acceptable Daily Intake of 0.56 µg/kg body weight/day established by DPH for fish advisory purposes would not be appropriate to use as a justification for higher allowable levels of mercury waste disposal into Alaska's environment. The chronic oral Acceptable Daily Intake of 0.56 µg/kg body weight/day should not be used for regulatory purposes. Instead, the dependence of many Alaska residents on subsistence fish harvests argues for sustained or enhanced protection of Alaska's environment from mercury pollution relative to national standards. A significant portion of Alaska's population depends on fish consumption, and Alaskans consume larger quantities of fish than the average American does. We have provided evidence of the types of adverse health effects that could occur if Alaskans were compelled to reduce fish consumption due to contaminant concerns. To maintain clean, healthy fish stocks upon which the health of many Alaskans depend, Alaska must protect its environment from mercury pollution.

Fish Consumption Guidance for the State of Alaska

Based on the decisions of the Alaska Scientific Advisory Committee for Fish Consumption, DPH has developed a series of fish consumption recommendations. These are explained in detail below.

First, DPH used a risk-based method to calculate monthly consumption allowances for Alaska-caught fish, by using our Alaska-specific Acceptable Daily Intake of 0.56 µg/kg body weight/day and a meal size of 6 ounces (raw) (Table 6).

Table 6. Alaska-Caught Fish Monthly Consumption Allowances for Women Who are or Can Become Pregnant, Nursing Mothers, and Children

***Categorizations below assume all mercury is methylmercury (MeHg) in Alaska fish**		
Fish MeHg Conc, ppm wet weight	**Meals**	**Species**
0–0.20	**Unrestricted**	Arctic cisco Big skate Black rockfish Broad whitefish Dolly Varden Dusky rockfish Grayling Halibut <40 pounds Humpback whitefish Least cisco Lingcod <35 inches Pacific Cod Pacific ocean perch Rainbow trout Rougheye rockfish Sablefish Salmon, Chinook (King) Salmon, Chum Salmon, Pink Salmon, Red (Sockeye) Salmon, Silver (Coho) Sheefish Walleye pollock
>0.20–0.34	**16**	Halibut 40 – 80 pounds Lake trout Lingcod 35– 40 inches
>0.34–0.46	**12**	Halibut 80 – 140 pounds Lingcod 40– 45 inches Longnose Skate
>0.46–0.68	**8**	Yelloweye rockfish Halibut 140 – 220 pounds
>0.68–1.36	**4**	Halibut > 220 pounds Lingcod > 45 inches Salmon shark Spiny dogfish

Notes:
-Calculations performed using 6 ounce meal size, and Acceptable Daily Dose of 0.56 µg/kg BW/day established by the Alaska Scientific Advisory Committee for Fish Consumption
-Calculations assume a single-species diet
-Guidelines remain "unrestricted consumption of all fish from Alaska Waters" for groups other than women who are or can become pregnant, nursing mothers, and children
-Halibut filet mercury concentration data are also presented by fish length in Table 3a

Although states consistently limit mercury exposures from fish consumption among women of childbearing age and "young children," the states and other agencies have inconsistent age cut-offs for "young children". The concern is that mercury affects the developing brain, and a child's brain continues to develop at a relatively rapid pace through adolescence and further "brain wiring" continues likely into adulthood (Lebel and Beaulieu, 2011). However, there are no definitive studies linking low-level postnatal mercury exposures from fish consumption with cognitive deficits, so the age at which sensitivity to mercury is passed is unknown. For the purpose of these guidelines, we consider children to be <18 years of age.

In cases where women and children are advised to limit consumption of a particular species, they are encouraged to substitute that species with fish that have lower tissue concentrations of mercury, such as salmon, arctic cisco, big skate, black rockfish, broad whitefish, Dolly Varden, dusky rockfish, grayling, halibut <40 pounds, humpback whitefish, least cisco, lingcod <35 inches, Pacific cod, Pacific ocean perch, rainbow trout, rougheye rockfish, sablefish, sheefish, and walleye pollock. If they cannot obtain these fish, communities are encouraged to substitute the fish species to be avoided with a healthful protein alternative.

Recreational fishers are a target audience for Alaska's fish consumption guidelines, as they are most likely to eat multiple meals from a large individual fish that may have a high mercury level (*e.g.*, shark species or very large halibut). The Alaska Scientific Advisory Committee for Fish Consumption plans to work with the ADF&G to incorporate fish consumption guidelines into their annual Sport Fishing Regulations booklets. Fishers who are concerned about mercury levels in the large halibut they catch are encouraged to have their fish analyzed for mercury, so DPH can provide individualized advice about the maximum amount of that fish sensitive family members are suggested to eat each month. While some large halibut from Alaska have mercury levels high enough to warrant consumption restrictions for sensitive populations, some do not have high mercury levels and are safe to eat in larger quantities.

It is important to note that most halibut caught in Alaska are relatively small, and these smaller halibut do not contain mercury at levels of health concern. In 2013, the average size of a recreationally-caught halibut in Alaska ranged from 16 pounds to 22 pounds. Similarly, the average size of a subsistence-caught halibut in Alaska in 2012 was 24 pounds (IPHC, 2014a). The average size of a commercially-caught halibut from Alaska waters in 2013 was 32 pounds (IPHC, 2014b).

Consumers of store- or restaurant-bought fish are encouraged to eat more fish, particularly fish that are lower in mercury, for their important health benefits. Very few commercial fish from Alaska are affected by the Alaska fish consumption guidelines. Most Alaska fish species, including all five wild Alaska salmon species, are very low in mercury and are safe to eat in unrestricted quantities. Women of childbearing age and children may enjoy unrestricted store- or restaurant-bought halibut meals per month, as the average weight of commercially-caught halibut in Alaska is only 32 pounds and does not contain mercury at levels of health concern. On occasion, lingcod, yelloweye rockfish, and spiny dogfish may also be available commercially. Consumers of those fish species are advised to follow the fish consumption guidelines outlined in Table 6.

DPH encourages health care providers to promote fish consumption as a healthy dietary choice, and a tool to reduce the risks associated with several common chronic diseases. Special information is being developed for health care providers who treat pregnant patients. It is important for health care providers to know that fish consumption contributes significantly to optimal fetal brain development, so that patients are not mistakenly advised to avoid fish consumption due to mercury or other concerns. Obstetricians and other health care providers are being informed about Alaska fish species with low mercury levels, Alaska fish species with the highest omega-3 fatty acid levels (and thus the greatest potential benefit to the developing fetus), and Alaska fish species that should be consumed sparingly during pregnancy.

Data Gaps and Future Research Priorities

The Alaska Scientific Advisory Committee for Fish Consumption has identified a number of data gaps and research priorities for the future. These include:

- There are insufficient human biomonitoring data currently available. The statewide surveillance program for women of childbearing age should be continued indefinitely to inform public health officials about trends of mercury exposure among locations and through time. The Section of Epidemiology should perform more targeted projects among individual communities with the potential for higher mercury exposures, to ensure that no Alaskans incur exposure to mercury at levels of concern.
- There are insufficient data on fish consumption rates and practices among urban Alaskans.
- There are insufficient data on mercury levels in Alaska-caught halibut. More information is needed to learn about location-specific trends, time trends, size/mercury concentration relationships, feeding ecology, and gender-specific information about mercury levels. In addition, more halibut in the large size classes (>50 pounds) need to be tested in order to better characterize mercury concentrations in these fish.
- There are insufficient data on omega-3 fatty acid levels and other nutrients in each Alaska fish species. These data are needed to effectively incorporate benefit information into our fish consumption advice.
- There are insufficient sample sizes or no baseline data for many Alaska fish species, including herring, eulachon (hooligan), blackfish, tomcod, smelt, kelp greenling, rock greenling, Atka mackerel, copper rockfish, quillback rockfish, silvergrey rockfish, yellowtail rockfish, red Irish lord, yellow Irish lord, northern rock sole, blue shark, Arctic char, round whitefish, and longnose sucker.
- There are insufficient data on mercury levels in king crab and other shellfish from Alaska waters.
- There are insufficient data on fish from inland waters of Alaska. Variation in mercury content among fish in different watersheds is likely, making this a challenging task. Data on pike and burbot are available, but additional monitoring efforts should focus on other long-

lived resident freshwater species such as whitefish, lake trout, blackfish, cisco, sheefish, and char.

General Guidelines to Minimize Exposure to Contaminants from Fish

In addition to the mercury-specific guidelines discussed in this document, there are a number of general things people can do to minimize their exposure to mercury or other contaminants in fish. These include:

- Keep smaller fish for eating (subject to minimum size limit regulations). In addition to tasting better, younger, smaller fish have had less time to accumulate mercury and other contaminants than older, larger fish. Selection of smaller fish for eating reduces health risks due to mercury exposure.
- Eat smaller meals when you eat big fish, and eat big fish less often. Freeze part of your catch to space the meals out over time.
- In cases where women and children are advised to limit consumption of a particular species, they are encouraged to substitute that species with fish that have lower tissue concentrations of mercury, such as salmon, arctic cisco, big skate, black rockfish, broad whitefish, Dolly Varden, dusky rockfish, grayling, halibut <40 pounds, humpback whitefish, least cisco, lingcod <35 inches, Pacific cod, Pacific ocean perch, rainbow trout, rougheye rockfish, sablefish, sheefish, and walleye pollock. If they cannot obtain these fish, communities are encouraged to substitute the fish species to be avoided with a healthful protein alternative.

By following these recommendations, Alaskans can enjoy the many benefits of fish consumption while minimizing the risk of adverse health effects due to contaminant exposure.

References

Alaska Department of Commerce, Community, and Economic Development . 2007. Alaska Seafood Industry Fish Facts. 6-12-2007.

Alaska Department of Environmental Conservation Radiation Page. 2014. http://dec.alaska.gov/eh/Radiation/index.html

Alaska Department of Fish and Game. Commissioner welcomes Governor's signature on sport fish guide bill. Alaska Department of Fish and Game. 6-16-2004. Juneau, AK. Press Release. 6-12-2007.

Alaska Department of Fish and Game. Cook Inlet personal use fisheries: Important information. Alaska Department of Fish and Game. 2007. 6-11-2007.

ADFG 2010 Alaska Department of Fish and Game, 2010, Subsistence in Alaska—A Year 2010 Update: Alaska Department of Fish and Game, Division of Subsistence

Alaska Department of Health and Social Services Environmental Public Health Program. 2011. http://www.epi.hss.state.ak.us/eh/fish/MidKuskoPikeBurbotFactSheetJune2011.pdf

Alaska Department of Health and Social Services Obesity Prevention and Control Program. 2014a. http://dhss.alaska.gov/dph/Chronic/Pages/Obesity/default.aspx (Accessed on April 7, 2014).

Alaska Department of Health and Social Services Environmental Public Health Program Radiation Page. 2014b. http://www.epi.hss.state.ak.us/eh/radiation/default.htm

ADOL, 2011. http://labor.alaska.gov/trends/nov11.pdf

Alaska Division of Public Health. Mercury and national fish advisories–Recommendations for fish consumption in Alaska. *Epidemiology Bulletin*. 2001. http://www.epi.hss.state.ak.us/bulletins/docs/b2001_06.htm

Alaska Division of Public Health. Age-adjusted diabetes prevalence, Alaska (AK BRFSS) and US (NHIS), 1996 - 2005. Alaska Diabetes Prevention and Control Program . 2007. 6-8-2007.

Alaska Division of Public Health. 2014. Fish Consumption Calculator. Accessible at http://www.epi.alaska.gov/eh/fish/fishconsumptioncalc.pdf

Allen BC, Kavlock RJ, Kimmel CA, Faustman EM. 1994. Dose-response assessment for developmental toxicity. II. Comparison of generic benchmark dose estimates with no observed adverse effect levels.

Ames BN, Magaw R, Gold LS. Ranking possible carcinogenic hazards. Science. 1987;236:271-280.

AMAP. AMAP Assessment 2002: Human Health in the Arctic. 2003. Oslo, Norway, AMAP.

AMAP. Arctic Pollution 2002. 111. 2002. Oslo, Arctic Monitoring and Assessment Programme.

Arnold SM, Lynn TV, Verbrugge LA, Middaugh JP. Human biomonitoring to optimize fish consumption advice: Reducing uncertainty when evaluating benefits and risks. *American Journal of Public Health.* 2005;95:393-397.

Axelrad DA, Bellinger DC, Ryan LM, Woodruff TJ.2007. Dose-response relationship of prenatal mercury exposure and IQ: an integrative analysis of epidemiologic data. *Environ Health Perspect*. 115(4):609-15.

Bakir F, Damluji SF, Amin-Zaki L *et al* Methylmercury poisoning in Iraq. *Science*. 1973;181:230-241.

Ballew, C., Ross, A., Wells, R. S., Hiratsuka, V., Hamrick, K. J., Nobmann, E. D., and Bartell, S. Final report on the Alaska Traditional Diet Survey. 2004. Anchorage, AK. Alaska Native Health Board.

Bersamin A, Luick BR, King IB, Stern JS, Zidenberg-Cherr S. 2008. Westernizing diets influence fat intake, red blood cell fatty acid composition, and health in remote Alaskan Native communities in the center for Alaska Native health study. *J Am Diet Assoc*. 108(2):266-73.

Boucher O, Bastien CH, Saint-Amour D, Dewailly E, Ayotte P, Jacobson JL, Jacobson SW, Muckle G. 2010. Prenatal exposure to methylmercury and PCBs affects distinct stages of information processing: an event-related potential study with Inuit children. Neurotoxicology. 31(4):373-84

Boucher O, Burden MJ, Muckle G, Saint-Amour D, Ayotte P, Dewailly E, Nelson CA, Jacobson SW, Jacobson JL. 2011. Neurophysiologic and neurobehavioral evidence of beneficial effects of prenatal omega-3 fatty acid intake on memory function at school age. Am J Clin Nutr. 93(5):1025-37

Boucher O, Jacobson SW, Plusquellec P, Dewailly E, Ayotte P, Forget-Dubois N, Jacobson JL, Muckle G. 2012a. Prenatal methylmercury, postnatal lead exposure, and evidence of attention deficit/hyperactivity disorder among Inuit children in Arctic Québec. Environ Health Perspect. 120(10):1456-61.

Boucher O, Burden MJ, Muckle G, Saint-Amour D, Ayotte P, Dewailly É, Nelson CA, Jacobson SW, Jacobson JL. 2012b. Response inhibition and error monitoring during a visual go/no-go task in inuit children exposed to lead, polychlorinated biphenyls, and methylmercury. Environ Health Perspect. 120(4):608-15.

Budtz-Jorgensen E, Keiding N, Grandjean P, White RF, Weihe P. Methylmercury neurotoxicity independent of PCB exposure. *Environ Health Perspect*. 1999;107:A236-A237.

Budtz-Jørgensen E, Keiding N, Grandjean P. 2004. Effects of exposure imprecision on estimation of the benchmark dose. Risk Anal. 24(6):1689-96.

Cernichiari E, Toribara TY, Liang L *et al* The biological monitoring of mercury in the Seychelles study. *NeuroToxicology*. 1995;16:613-628.

Clarkson TW, Strain JJ. Nutritional factors may modify the toxic action of methyl mercury in fish-eating populations. *J Nutrition*. 2003;133:1539S-1543S.

Clewell, H.J., J.M. Gearhart, P.R. Gentry, T.R. Covington, C.B. VanLandingham, K.S. Crump, and A.M. Shipp. 1999. Evaluation of the uncertainty in an oral reference dose for methylmercury due to inter-individual variability in pharmacokinetics. Risk Anal. 19(4):547-558.

Cohen JT, Bellinger DC, Shaywitz BA. 2005. A quantitative analysis of prenatal methyl mercury exposure and cognitive development. Am J Prev Med. 29(4):353-65.

Covello VT, Merkhofer MW. *Risk Assessment Methods Approaches for Assessing Health and Environmental Risks*. New York: Plenum Press; 1993.

Crump KS. 1984. A new method for determining allowable daily intakes. Fundam Appl Toxicol. 4(5):854-71.

Crump KS, Kjellström T, Shipp AM, Silvers A, Stewart A. 1998. Influence of prenatal mercury exposure upon scholastic and psychological test performance: benchmark analysis of a New Zealand cohort. *Risk Anal*. 18(6):701-13.

Davidson PW, Myers GJ, Cox C et al Neurodevelopmental test selection, administration, and performance in the main Seychelles child development study. NeuroToxicology. 1995;16:665-676.

Davidson PW, Myers GJ, Cox C et al Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment. JAMA. 1998;280:701-707.

Davidson PW, Cory-Slechta DA, Thurston SW, Huang LS, Shamlaye CF, Gunzler D, Watson G, van Wijngaarden E, Zareba G, Klein JD, Clarkson TW, Strain JJ, Myers GJ. 2011. Fish consumption and prenatal methylmercury exposure: cognitive and behavioral outcomes in the main cohort at 17 years from the Seychelles child development study. Neurotoxicology. 32(6):711-7

Debes F, Budtz-Jørgensen E, Weihe P, White RF, Grandjean P. 2006. Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years. Neurotoxicol Teratol. 28(5):536-47.

Dewailly E, Blanchet C, Lemieux S *et al.* N-3 Fatty acids and cardiovascular disease risk factors among the Inuit of Nunavik. Am J Clin Nutr. 2002;74:464-473.

Dorea JG. Fish are central in the diet of Amazonian riparians: should we worry about their mercury concentrations? *Environmental Research*. 2003;92:232-244.

Ebbesson SOE, Adler AI, Risica PM *et al.* Cardiovascular disease and risk factors in three Alaskan Eskimo populations: the Alaska-Siberia project. *Int J Circumpolar Health.* 2005;64:365-386.

Egeland GM, Middaugh JP. Balancing fish consumption benefits with mercury exposure. Science. 1997;278:1904-1905.

Feeley, M.M. and Lo, M.-T. Risk Assessment for Mercury in Health Canada - Development of the Provisional Tolerable Daily Intake (pTDI) Value. In: Proceedings of the Conference on Mercury in Eastern Canada and the Northeast States, 21-23 September, 1998. Ed. by Pilgrim, W., Burgess, N., Giguère, M.-F. 1998. Unpublished.

Fisher NS, Beaugelin-Seiller K, Hinton TG, Baumann Z, Madigan DJ, Garnier-Laplace J. 2013. Evaluation of radiation doses and associated risk from the Fukushima nuclear accident to marine biota and human consumers of seafood. Proc Natl Acad Sci U S A. 110(26): 10670–10675.

FAO/WHO. Food and Agriculture Organization of the United Nations/World Health Organization. 2011. Report of the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption. Rome, Food and Agriculture Organization of the United Nations;

Geneva, World Health Organization, 50 pp.

Friberg L. Methylmercury in fish: A toxicological-epidemiological evaluation of risks report from an expert group. *Nord Hyg Tidskr*. 1971;4 (Suppl):19-364.

Gillum RF, Mussolino M, Madans JH. The relation between fish consumption, death from all causes, and incidence of coronary heart disease: the NHANES I Epidemiologic Follow-up Study. *J Clin Epidemiol*. 2000;53:237-244.

Goldsmith, S., Howe, L., Angvik, J., Leask, L., and Hill, A. Status of Alaska Natives 2004. 2004. Anchorage, AK, Institute of Social and Economic Research, University of Alaska Anchorage. Accessed on 4/24/2014 at http://www.iser.uaa.alaska.edu/Publications/StatusAKNativessumm.pdf

Grandjean P, Weihe P, Jorgensen PJ, Clarkson T, Cernichiari E, Videro T. Impact of maternal seafood diet on fetal exposure to mercury, selenium, and lead. *Archives of Environmental Health*. 1992;47:185-195.

Grandjean P, Weihe P, Nielsen JB. Methylmercury: significance of intrauterine and postnatal exposures. *Clin Chem*. 1994;40:1395-1400.

Grandjean P, Weihe P, White RF, Debes F. Cognitive performance of children prenatally exposed to "safe" levels of methylmercury. *Environ Res*. 1998;77:165-172.

Grandjean P, Weihe P, White RF *et al* Cognitive deficit in 7-year old children with prenatal exposure to methylmercury. *Neurotoxicology and Teratology*. 1997;19:417-428.

Grandjean P, Weihe P, Burse VW *et al* Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. *Neurotoxicology and Teratology*. 2001;23:305-317.

Haley, Sharman, Berman, Matthew, Goldsmith, Scott, Hill, Alexandra, and Kim, Hongjin. Economics of Sport Fishing in Alaska. 1999. Anchorage, AK, Institute of Social and Economic Research.

Hanson DJ. Dioxin toxicity: new studies prompt debate, regulatory action. *Chemical & Engineering News*. 1991;7-14.

Hartman, Jeff. Economic impact analysis of the seafood industry in Southeast Alaska: Importance, personal income, and employment in 1994. 5J02-07. 10-16-2002. Juneau, AK, Alaska Department of Fish and Game. Regional Information Report.

He K, Xun P, Liu K, Morris S, Reis J, Guallar E. 2013. Mercury exposure in young adulthood and incidence of diabetes later in life: the CARDIA Trace Element Study. Diabetes Care. 36(6):1584-9.

Hibbeln JR, Davis JM, Steer C, Emmett P, Rogers I, Williams C, Golding J. 2007. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. Lancet. 369(9561):578-85.

Homer RD, Day GM, Lanier AP, *et al.* 2009. Stroke mortality among Alaska Native people. *Am J Public Health*.99:1996-2000.

Institute of Medicine of the National Academies. *Seafood choices: Balancing benefits and risks*. Washington DC: National Academies Press; 2007.

IPHC. 2014a http://www.iphc.int/meetings/2014am/SubsistenceHalibutHarvestsIPHC2014.pdf

IPHC. 2014b. http://www.iphc.int/publications/rara/2013/rara2013.pdf IPHC, 2014 Report of Research and Assessment Activities, 2013

JECFA. WHO Food Additives Series:44. Safety evaluation of certain food additives and contaminants. Methylmercury. 2000. Geneva, Fifty-third Meeting of the Joint FAO/WHO Expert Committee on Food Additives.

Jensen, Pia G. and Nobmann, Elizabeth. What's in Alaskan Foods. 1994. Anchorage, Alaska, Nutrition Services, Alaska Area Native Health Service, U. S. Department of Health and Human Services, Indian Health Service, Alaska Area Native Health Service. 1994.

Johnston JM, Day GE, Veazie MA, Provost E. 2011. Heart disease mortality among Alaska Native people, 1981-2007. Public Health Rep. 126(1):73-83.

Kimmel CA, Kavlock RJ, Allen BC, Faustman EM. 1995. The application of benchmark dose methodology to data from prenatal developmental toxicity studies. Toxicol Lett. 82-83:549-54.

Kinjo Y, Takizawa Y, Shibata Y, Watanabe M, Kato H. Threshold dose for adults exposed to methylmercury in Niigata Minamata Disease Outbreak. *Environmental Sciences*. 1995;3:91-101.

Klaunig JE. Chemical Carcinogenesis. In: Klaassen CD, ed. *Casarett & Doull's Toxicology - The basic science of poisons*. Eighth Ed. New York: McGraw-Hill; 2013:393-443.

Kuhnlein HV, Receveur O, Chan HM. Traditional food systems research with Canadian Indigenous Peoples. *International Journal of Circumpolar Health*. 2001;60:112-122.

Kutsuna, Masachika. Minamata Disease. 1968. Study Group of Minamata Disease. Kumamoto University, Japan. 1968.

Lanier, A. P., Ehrsam, G., and Sandidge, J. Alaska Native mortality 1989-1998. 2002. Office of Alaska Native Health Research, Division of Community Health Services, Alaska Native Tribal Health Consortium.

Lebel C, Beaulieu C. 2011. Longitudinal development of human brain wiring continues from childhood into adulthood. J Neurosci. 31(30): 10937-47.

Madigan DJ, Baumann Z, and Fisher NS. 2012. Pacific bluefin tuna transport Fukushima-derived radionuclides from Japan to California. Proc Natl Acad Sci U S A. 109(24): 9483–9486.

Madigan DJ, Baumann Z, Snodgrass OE, Ergül HA, Dewar H, Fisher NS. 2013. Radiocesium in Pacific Bluefin Tuna Thunnus orientalis in 2012 Validates New Tracer Technique. Environ Sci Technol. 47(5):2287-94.

Makhoul Z, Kristal AR, Gulati R, Luick B, Bersamin A, O'Brien D, Hopkins SE, Stephensen CB, Stanhope KL, Havel PJ, Boyer B. 2011. Associations of obesity with triglycerides and C-reactive protein are attenuated in adults with high red blood cell eicosapentaenoic and docosahexaenoic acids. *Eur J Clin Nutr.* 65(7):808-17.

Marsh DO, Clarkson TW, Cox C, Myers G, Amin-Zaki J, Al-Tikriti S. Fetal methylmercury poisoning: relationship between concentration in single strands of maternal hair and child effects. *Archives of Neurology*. 1987;44:1017-1022.

Marsh DO, Clarkson TW, Myers GJ *et al* The Seychelles study of fetal methylmercury exposure and child development: introduction. *NeuroToxicology*. 1995;16:583-596.

Martin, 2012. http://www.iser.uaa.alaska.edu/Publications/2012-ImportanceOfCultureCommunityWellBeing.pdf

Martin and Hill 2009 http://www.iser.uaa.alaska.edu/Publications/webnote/WebNote5.pdf

McFarland VA, Clarke JU. 1989. Environmental occurrence, abundance, and potential toxicity of polychlorinated biphenyl congeners: considerations for a congener-specific analysis. *Environmental Health Perspectives*. 81:225-239.

McLaughlin JB, Middaugh JP, Utermohle CJ, Asay ED, Fenaughty AM, Eberhart-Phillips JE. Changing patterns of risk factors and mortality for coronary heart disease among Alaska Natives, 1979-2002. *JAMA*. 2004;291:2545-2546.

Merrill, T; Opheim, M. 2013. Assessment of Cook Inlet Tribes Subsistence Consumption. Prepared for Seldovia Village Tribe Council. Published on September 30, 2013.

Middaugh, John P. Cardiovascular Disease in Alaska. January 13, 1997. State of Alaska, Alaska Division of Public Health. *Epidemiology Bulletin* 1997. http://www.epi.hss.state.ak.us/bulletins/docs/b1997_03.htm

Middaugh, John P. Physical Activity and Health in Alaska. January 17, 1997. State of Alaska, Alaska Division of Public Health. *Epidemiology Bulletin* 1997. http://www.epi.hss.state.ak.us/bulletins/docs/b1997_04.htm

Mozaffarian D, Peilin Shi, J. Steven Morris, Donna Spiegelman, Philippe Grandjean, David S. Siscovick, Walter C. Willett, Eric B. Rimm. Mercury Exposure and Risk of Cardiovascular Disease in Two U.S. Cohorts. N Engl J Med. 2011 March 24; 364(12): 1116–1125.

Mozaffarian D, Peilin Shi, J. Steven Morris, Philippe Grandjean, David S. Siscovick, Donna Spiegelman, Walter C. Willett, Eric B. Rimm, Gary C. Curhan, John P. Forman Mercury Exposure and Risk of Hypertension in US Men and Women in Two Prospective Cohorts. Hypertension. 2012 September; 60(3): 645–652

Moon SS. 2013. Association of lead, mercury and cadmium with diabetes in the Korean population: the Korea National Health and Nutrition Examination Survey (KNHANES) 2009-2010. Diabet Med. 30(4):e143-8.

Mordukhovich I, Wright RO, Hu H, Amarasiriwardena C, Baccarelli A, Litonjua A, Sparrow D, Vokonas P, Schwartz J. 2012. Associations of toenail arsenic, cadmium, mercury, manganese, and lead with blood pressure in the normative aging study. Environ Health Perspect. 120(1):98-104.

Mouratoff GJ, Carroll NV, Scott EM. Diabetes mellitus in Eskimos. *Journal of the American Medical Association*. 1967;199:107-112.

Mouratoff GJ, Scott EM. Diabetes Mellitus in Eskimos after a decade. *Journal of the American Medical Association*. 1973;226:1345-1346.

Murata K, Weihe P, Budtz-Jorgensen E, Jorgensen PJ, Grandjean P. Delayed brainstem auditory evoked potential latencies in 14-year-old children exposed to methylmercury. *J Pediatr*. 2004;144:177-183.

Murphy NJ, Schraer CD, Theile MC *et al*. Hypertension in Alaska Natives: association with overweight, glucose intolerance, diet and mechanized activity. *Ethnicity & Health*. 1997;2:267-275

Myers G, Davidson P, Cox C *et al* Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. *The Lancet*. 2003;361:1686-1692.

Myers GJ, Davidson PW, Shamlaye C, Cox C, Kost J, Beck C, Huang L, Weiss B. The Seychelles Child Development Study of methyl mercury from fish consumption: analysis of subscales from the Child Behavior Checklist at age 107 months in the main cohort. Seychelles Medical Dental Journal 2004;7:107–114.

Myers GJ, Thurston SW, Pearson AT, Davidson PW, Cox C, Shamlaye CF, Cernichiari E, Clarkson TW. 2009. Postnatal exposure to methyl mercury from fish consumption: a review and new data from the Seychelles Child Development Study.Neurotoxicology. 30(3):338-49.

Narayanan ML, Schraer CD, Bulkow LR, Koller KR, Asay E, Mayer AM, Raymer TW. 2010. Diabetes prevalence, incidence, complications and mortality among Alaska Native people 1985-2006. Int J Circumpolar Health. 69(3):236-52

National Research Council. *Toxicological effects of methylmercury*. Washington DC: National Academy Press; 2000.

NIEHS (National Institute of Environmental Health Sciences). Scientific issues relevant to assessment of health effects from exposure to methylmercury. 1998. Report from Workshop, November 10-18, 1998, Raleigh NC.

Nielsen AB, Davidsen M, Bjerregaard P. 2012. The association between blood pressure and whole blood methylmercury in a cross-sectional study among Inuit in Greenland. Environ Health. 11:44.

Nobmann ED, Byers T, Lanier AP, Hankin JH, Jackson MY. The diet of Alaska Native adults: 1987-1988. *American Journal of Clinical Nutrition*. 1992;55:1024-1032.

Nobmann ED, Lanier AP. Dietary intake among Alaska native women resident of Anchorage, Alaska. *Int J Circumpolar Health.* 2001;60:123-137.

Nobmann ED, Ponce R, Mattil C, Devereux R, Dyke B, Ebbesson SO, Laston S, MacCluer J, Robbins D, Romenesko T, Ruotolo G, Wenger CR, Howard BV. 2005. Dietary intakes vary with age among Eskimo adults of Northwest Alaska in the GOCADAN study, 2000-2003. *J Nutr.* 135(4):856-62.

Pitot HC, Dragan YP. Chemical Carcinogenesis. In: Klaassen CD, ed. *Casarett & Doull's Toxicology - The basic science of poisons*. Fifth ed. New York: McGraw-Hill; 1996:201-267.

Receveur O, Boulay M, Kuhnlein HV. Decreasing Traditional Food Use Affects Diet Quality for Adult Dene/Métis in 16 Communities of the Canadian Northwest Territories. *J Nutr*. 1997;127:2179-2186.

Risica PM, Schraer C, Ebbesson SOE, Nobmann ED, Caballero B. Overweight and obesity among Alaskan Eskimos of the Bering Straits Region: the Alaska Siberia project. *International Journal of Obesity Related Metabolic Disorders* . 2000a. 24:939-944.

Risica PM, Ebbesson SOE, Schraer CD, Nobmann ED, Caballero BH. Body fat distribution in Alaskan Eskimos of the Bering Straits region: the Alaskan Siberia Project. *International Journal of Obesity Relat Metab Disord*. 2000b. 24:171-179.

Sagiv SK, Thurston SW, Bellinger DC, Amarasiriwardena C, Korrick SA. 2012. Prenatal exposure to mercury and fish consumption during pregnancy and attention-deficit/hyperactivity disorder-related behavior in children. Arch Pediatr Adolesc Med. 166(12):1123-31.

Sand S, Victorin K, Filipsson AF. 2008. The current state of knowledge on the use of the benchmark dose concept in risk assessment. J Appl Toxicol. 28(4):405-21.

Schraer CD, Lanier AP, Boyko EJ, Gohdes D, Murphy NJ. Prevalence of diabetes mellitus in Alaskan Eskimos, Indians, and Aleuts. *Diabetes Care*. 1988;11:693-700.

Schraer CD, Mayer AM, Vogt AM *et al.* The Alaska Native diabetes program. *Int J Circumpolar Health.* 2001;60:487-494

Schumacher MC, Slattery ML, Lanier AP, Ma KN, Edwards S, Ferucci ED, Tom-Orme L. 2008. Prevalence and predictors of cancer screening among American Indian and Alaska native people: the EARTH study. Cancer Causes Control. 19(7):725-37.

Scott EM, Griffith IV. Diabetes mellitus in Eskimos. *Metabolism*. 1957;6:320-325.

Shamlaye CF, Marsh DO, Myers GJ *et al* The Seychelles child development study on neurodevelopmental outcomes in children following in utero exposure to methylmercury from a maternal fish diet: background and demographics. *NeuroToxicology*. 1995;16:597-612.

Shkilnyk AM. *A Poison Stronger than Love: The Destruction of an Ojibwa Community*. New Haven: Yale University Press; 1985.

Shu HP, Paustenbach DJ, Murray FJ. A critical evaluation of the use of mutagenesis, carcinogenesis, and tumor promotion data in a cancer risk assessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Regulatory Toxicology and Pharmacology*. 1987;7:57-58.

Simopoulos AP. Omega-3 fatty acids in health and disease and in growth and development. *Am J Clin Nutr.* 1991;54:438-463.

Slattery ML, Schumacher MC, Lanier AP, Edwards S, Edwards R, Murtaugh MA, Sandidge J, Day GE, Kaufman D, Kanekar S, Tom-Orme L, Henderson JA. 2007. A prospective cohort of American Indian and Alaska Native people: study design, methods, and implementation. Am J Epidemiol. 166(5):606-15.

Southwick Associates Inc. and W.J. Romberg, A.E. Bingham, G.B. Jennings, and R.A. Clark. 2008. Economic impacts and contributions of sportfishing in Alaska, 2007. Alaska Department of Fish and Game, Professional Paper No. 08-01, Anchorage. Accessed on 4/9/2014 http://www.adfg.alaska.gov/fedaidpdfs/pp08-01.pdf

Stern, A.H. 1997. Estimation of the interindividual variability in the one-compartment pharmacokinetic model for methylmercury: implications for the derivation of a reference dose. Regul. Toxicol. Pharmacol. 25(3):277-288.

Swartout, J., and G. Rice. 2000. Uncertainty analysis of the estimated ingestion rates used to derive the methylmercury reference dose. Drug Clin. Toxicol. 23(1):293-306.

Uauy R, Valenzuela A. Marine oils: the health benefits of n-3 fatty acids. *Nutrition*. 2000;16:680-684..[106]

US ATSDR. Toxicological profile for mercury. 1999.

US Environmental Protection Agency. Guidance for assessing chemical contaminant data for use in fish advisories. Volume 3 - Overview of risk management. EPA 823-B-96-006. 1996.

US Environmental Protection Agency. Guidance for assessing chemical contaminant data for use in fish advisories Volume 1: Fish sampling and analysis. Third Edition. EPA 823-B-00-007. 2000.

US Environmental Protection Agency and US Food and Drug Administration. What you need to know about mercury in fish and shellfish. EPA-823-R-04-005. 2004.

Federal Register 79 FR 33559, Docket No. FDA-2014-N-0595.

U.S. FDA, 2013; Michael Landa, DOCKET FDA 2011 P 0484

UAF 2013 http://www.uaf.edu/files/ces/fcs/2013q2data.pdf

Usher, Peter J., Baikie, Maureen, Demmer, Marianne, Nakashima, Douglas, Stevenson, Marc G., and Stiles, Mark. Communicating About Contaminants in Country Food: The Experience in Aboriginal Communities. ISBN 0-9699774-0-9. 1995. Research Department Inuit Tapirisat of Canada. 1995.

Valera B, Dewailly E, Poirier P. 2008. Cardiac autonomic activity and blood pressure among Nunavik Inuit adults exposed to environmental mercury: a cross-sectional study. Environ Health. 7:29.

Valera B, Dewailly E, Poirier P. 2009. Environmental mercury exposure and blood pressure among Nunavik Inuit adults. Hypertension.54(5):981-6.

Valera B, Muckle G, Poirier P, Jacobson SW, Jacobson JL, Dewailly E. 2012. Cardiac autonomic activity and blood pressure among Inuit children exposed to mercury. Neurotoxicology. 33(5):1067-74.

Valera B, Dewailly E, Poirier P. 2013. Association between methylmercury and cardiovascular risk factors in a native population of Quebec (Canada): a retrospective evaluation. Environ Res. 120:102-8.

Virtanen JK, Mursu J, Voutilainen S, Uusitupa M, Tuomainen TP. 2014. Serum omega-3 polyunsaturated fatty acids and risk of incident type 2 diabetes in men: the Kuopio Ischemic Heart Disease Risk Factor study. Diabetes Care. 37(1):189-96.

Virtanen JK1, Nyantika AN, Kauhanen J, Voutilainen S, Tuomainen TP. 2012b. Serum long-chain n-3 polyunsaturated fatty acids, methylmercury and blood pressure in an older population. Hypertens Res. 35(10):1000-4.

Van Oostdam, J., Donaldson, S., Feeley, M., and Tremblay, N. Toxic substances in the Arctic and associated effects - Human health. 127. 2003. Ottawa, Indian and Northern Affairs Canada. Northern Contaminants Program, Canadian Arctic Contaminants Assessment Report II.

Van Oostdam JV, Gilman A, Dewailly E *et al.* Human health implications of environmental contaminants in Arctic Canada: a review. *Science of the Total Environment*. 1999;230:1-82.

van Wijngaarden E, Beck C, Shamlaye CF, Cernichiari E, Davidson PW, Myers GJ, Clarkson TW. 2006. Benchmark concentrations for methyl mercury obtained from the 9-year follow-up of the Seychelles Child Development Study. Neurotoxicology. 27(5):702-9

van Wijngaarden E, Thurston SW, Myers GJ, Strain JJ, Weiss B, Zarcone T, Watson GE, Zareba G, McSorley EM, Mulhern MS, Yeates AJ, Henderson J, Gedeon J, Shamlaye CF, Davidson PW. 2013. Prenatal methyl mercury exposure in relation to neurodevelopment and behavior at 19 years of age in the Seychelles Child Development Study. Neurotoxicol Teratol. 39:19-25

Wallin A, Di Giuseppe D, Orsini N, Patel PS, Forouhi NG, Wolk A. 2012. Fish consumption, dietary long-chain n-3 fatty acids, and risk of type 2 diabetes: systematic review and meta-analysis of prospective studies. Diabetes Care. 35(4):918-29.

Wheatley B. A new approach to assessing the effects of environmental contaminants on aboriginal peoples. *Arctic Medical Research*. 1994;53:386-390.

Wheatley, Margaret A. The social and cultural effects of environmental contaminants on Aboriginal peoples. 93-104. 1994. Yellowknife. 10-5-1994.

WHO. *Environmental Health Criteria 101: Methylmercury*. Geneva, Switzerland: World Health Organization; 1990.

Xun P1, Qin B, Song Y, Nakamura Y, Kurth T, Yaemsiri S, Djousse L, He K. 2012. Fish consumption and risk of stroke and its subtypes: accumulative evidence from a meta-analysis of prospective cohort studies. Eur J Clin Nutr. 66(11):1199-207.

Xun P, He K. 2012. Fish Consumption and Incidence of Diabetes: meta-analysis of data from 438,000 individuals in 12 independent prospective cohorts with an average 11-year follow-up. Diabetes Care. 35(4):930-8.

Yaginuma-Sakurai K1, Murata K, Shimada M, Nakai K, Kurokawa N, Kameo S, Satoh H. 2010. Intervention study on cardiac autonomic nervous effects of methylmercury from seafood. Neurotoxicol Teratol. 32(2):240-5.

Yorifuji T1, Tsuda T, Kashima S, Takao S, Harada M. 2010. Long-term exposure to methylmercury and its effects on hypertension in Minamata. Environ Res. 110(1):40-6.

Yoshizawa K1, Rimm EB, Morris JS, Spate VL, Hsieh CC, Spiegelman D, Stampfer MJ, Willett WC. 2002. Mercury and the risk of coronary heart disease in men. N Engl J Med. 347(22):1755-60.

APPENDIX

Neurodevelopmental Endpoints

Table. Studies that assessed the neurodevelopmental effects of mercury ingestion from fish

Study	Cohort year/time	Study Type	Population Type and Cohort Size	Endpoint Examined	Exposure Assessment	Adverse Effects Yes/No	LOAEL/NOAEL
Grandjean, Debes, *et al*	Faroe Islands	Prospective Cohort	1,023 child-mother pairs	Neurodevelopmental Outcomes	Hair mercury; Blood mercury	Yes. Subtle effects	LOAEL ≥58 ppb blood mercury
Myers, Davidson, van Wijngaarden *et al*	Seychelles Islands	Prospective Cohort	779 child-mother pairs	Neurodevelopmental Outcomes	Hair mercury	No	NOAEL =15 ppm in hair
Crump, Kjellstrom *et al.*	New Zealand	Prospective Cohort	237 child-mother pairs	Neurodevelopmental Outcomes	Hair mercury	Yes, subtle effects.	LOAEL ≥4 ppm hair mercury
Sagiv *et al.*	New Bedford, MA	Prospective Cohort	515 child-mother pairs	Neurodevelopmental Outcomes	Hair mercury; Fish consumption	Mixed Effects.	LOAEL ≥1 ppm hair mercury
Boucher *et al.*	Nunavik, Arctic Quebec	Prospective Cohort and Crossectional	118–279 children and/or children-mother pairs	Neurodevelopmental Outcomes	Hair mercury; Blood mercury	Mixed Effects.	Variable

Cardiovascular Outcomes

Table. Studies that assessed the effect of mercury ingestion from fish on cardiovascular risk

Study	Study Type	Population and Study Dates/Follow-up length	Cohort Size	Endpoint Examined	Exposure Assessment	Adverse Effect Yes/No	LOAEL/NOAEL	Comments
Mozaffarian *et al* 2012	Two prospective cohorts (51,529 males in the Health Professionals Follow-up study and 121,700 women in the Nurses' Health Study) Study) (Nested Case-Control Study)	Adult US men (and women. Average 14.9 years of followup	6,045	Incident Hypertension	Toenail mercury. 1987 samples from men (professionals study) and 1982–3 from women in nurses' study. Toenail Hg highest quintile = 0.74 ppm (~2.0 ppm in hair). Highest tertile = 1.06 ppm	No.	NOAEL quintile >0.74 ppm toenail mercury (~2.0 ppm in hair) NOAEL tertile >1.06 ppm toenail mercury (~2.5 ppm in hair)	No risk of incident hypertension in highest *vs*. lowest exposure quintile. RR, 0.94 (0.84–1.06) for men and women combined (0.96 (0.84–1.09 in women and 0.82 (0.62–1.08) in men. Study shows protective effect when stratified by deciles as opposed to quintiles (p-trend = 0.01, 0.02, and 0.03 with increasing toenail mercury after adjustment for 1) age and sex; 2) multiple variables; and 3) multiple variables and diet-adjustment, respectively.
Mozaffarian *et al*., 2011	Two prospective cohorts (51,529 males in the Health Professionals Follow-up study and 121,700 women in the Nurses' Health	Adult US men (and women. Average 11.3 years of age	3,427	Coronary Heart Disease and Stroke	Toenail mercury. 1987 samples from men (professionals study) and 1982–3 from women in nurses' study. 0.3 ppm median in	No.	NOAEL >0.84 ppm toenail Hg (~2.1 ppm in hair)	Mercury concentrations were associated with reduction in trend of relative risks with increasing quintiles of toenail mercury for coronary heart diseases and total cardiovascular diseases, but not in stroke incidence in men and women combined,

	Study) (Nested Case-Control Study)				cases and 0.31 in controls of men and 0.21 *vs* 0.23, respectively in women.			although the significance was achieved for trend in only one of two models. Significance disappeared after adjustment for more CVD risk factors such as BMI, physical activity, alcohol intake, diabetes, hypertension, elevated cholesterol, and estimated eicosapentaenoic and docosahexaenoic acid.
Valera *et al.* 2013	Crossectional study on adult Inuit men and women in 14 villages of Nunavik in arctic Quebec	132 men and 181 women (>18 y, mean age 38 y)	313	HR, BP	Blood mercury geometric mean = 15.4 μg/l.	Mixed. No for BP. Yes for resting HR.	For BP, NOAEL >15.4 μg/L mercury in blood (~4 ppm in hair). For HR, LOAEL = 29.4 μg/L mercury in blood (~7.5 ppm in hair).	In adjusted models, higher blood mercury associated with decreased diastolic blood pressure, while systolic and PP were not significantly associated after adjustment for varying factors. Adjustment not consistent across BP indices. Resting HR significantly positively associated with blood mercury.
Valera *et al.* 2009	Crossectional Study on adult Inuit men and women in 14 villages of Nunavik in arctic Quebec	Men and women (>18 y, mean age 34.3 y) in Fall 2004	732	BP	Blood mercury mean = 50.2 nmol/L (~ 5 ppm Hg in hair)	Yes	Cannot be determined. LOAEL <50.2 nmol/L Hg in blood	In multivariate adjusted models, mercury was associated with systolic BP (beta = 2.14, p=0.0004) but not diastolic (beta =0.96, p=0.069). Participant salt intake not assessed (only 24-hour dietary recall). Testing occurred on an ice breaker ship. Crossectional study.

Valera *et al.* 2008	Crossectional Study on adult Inuit men and women in 14 villages of Nunavik in arctic Quebec	85 men and 120 women (>40 y, mean age 52.1 y) in Fall 2004	280	2-hr Holter monitor data (BP, LF, SDANN, SDNN, CVRR)	Blood mercury arithmetic mean = 133.2 nmol/L (27 μg/L ~ 6.5 ppm in hair) and geometric mean = 97.8 nmol/L (19.6 μg/L ~ 5 ppm in hair)	Yes	Mixed results.	Adjustment for potential confounders resulted in associations between mercury in blood and SBP, PP, and SDANN, but not CVRR, LF, HF, LF/HF, NN, SDNN, rMSSD, pNN50%, or DBP.
Valera *et al.* 2012	Crossectional study on Inuit children from Nunavik villages	Inuit children (mean age = 11.6 years)	226	2-hr holter monitor and consecutive sphygmomanometer measurements	Cord blood mercury (median=81.5 nmoL/L) and blood (median=14.5 nmol/L) and hair mercury at 11 years of age (6.61 nmol/g).	No for prenatal and Mixed for 11 year time point HRV. No association between BP and cord blood Hg, 11 year old blood Hg, or 11 year old hair Hg.	NOAEL >81.5 nmol/L cord blood Hg for BP and HRV and >14.5 nmol/L in 11 year olds.for BP. NOAEL >6.61 nmol/g in 11-year old hair for BP and HRV. LOAEL =14.5 nmol/L for 11 year old blood HRV.	No association between any HRV parameter and prenatal mercury exposure. 11 y blood mercury associated with decreased LF (favorable outcome for health), decreased SDNN, decreased SDANN, and decreased CVRR but not LF/HF, HF, NN, or rMSSD. Hair Hg in children not associated with any HRV parameter.
Mordukhovich *et al.* (2012)	Crossectional sample from a longitudinal Veterans Administration Normative Aging Study	US adult men and women	639	BP	BP collected same day as toenail clippings (median mercury, 0.22 ppm), arsenic, cadmium, manganese, and lead)	No	NOAEL >0.22 ppm toenail mercury (~0.55 ppm in hair)	Arsenic (elevated) and manganese (lowered), but not mercury (no significant change), associated with statistically significant changes in blood pressure parameters.

Virtanen *et al.*, 2012a	Adults from the ongoing community-based longitudinal Kuopio Ischemic Heart Disease Risk Factor Study	Finnish adult men and women (age 53–73)	768	BP	Blood pressure, serum fatty acids, pubic hair mercury, dietary intake questionnaire	No	NOAEL >2 ppm hair mercury	Pulse pressure and SBP, but not DBP, were statistically significantly reduced in association with increasing quartiles of percent EPA+DPA+DHA quartiles in serum. BP not associated with hair mercury up to > 1.78 ppm [mean, 2.0 ppm (SD=1.9)], the highest exposure quartile
Virtanen *et al.*, 2012b	"	Finnish adult men (age 53–73)	1857 Finnish adult men (91 sudden cardiac deaths, SCD). Mean follow-up of 20.1 years.	SCD	Serum long chain n-3 PUFA and hair mercury concentration. Repeat hair samples were collected and mercury contents measured for 21 subjects 4 to 9 years (mean = 6 years) after the baseline examination.	Mixed. Association only when continuous outcomes considered, but not in tertiles. 3.25 ppm (highest tertile of hair mercury not significantly different from lowest tertile = 0.45 ppm	Not available	Used baseline measurements up to over 21 years from time of SCD. Serum fatty acids associated with lower risk of SCD at lower hair mercury concentrations. At higher mercury concentrations, there was a statistically significant trend of elevated SCD incidence with hair mercury concentrations (adjusted hazard ratio = 1.07 (95% CI, 1.03–1.11) per 0.5 ppm elevation in hair mercury concentration. Men with higher hair mercury more likely to smoke, live in a rural area, have less physical activity in leisure-time, lower education and income, and lower intake of fruits, berries, and vegetables.).
Nielsen *et al.*	Crosssectional population-	Adult Inuit men and	1,861	BP, Hypertension	Blood mercury	No	NOAEL >81 μg/L in blood	DBP lowered with increasing quintiles of

2012	based study among adult Inuit in Greenland (2005–2009)	women (age 30–69)			concentration. Mean whole blood mercury level = 20.5 μg/L among men and 14.7 μg/L among women.		(~20 ppm in hair)	blood mercury in men (5th quintile arithmetic mean blood mercury = 81.07 (95% C.I., 76.31–86.13 μg/L). Trend of lower risk of hypertension with elevated blood mercury. No meaningful effect in women.
Yoshizawa *et al.*, 2002	Nested case-control study in the prospective Health Professionals Followup Study in the U.S.	Adult men 40–75 years old	Toenail clippings provided in 1987 by 33,737 cohort members (470 incident Coronary Heart Disease cases	Coronary Heart Disease (CHD) (coronary-artery surgery, nonfatal MI, and fatal CHD). Five-year follow-up study.	Toenail mercury. Mean mercury levels similar in patients and controls (0.74 *vs.* 0.72 ppm, respectively). Median levels were 0.29, 0.34, 0.44, 0.62, and 0.75 ppm for increasing quintiles of fish consumption (median intake, 20.7, 26.1, 30.4, 37.2, and 51.0 g/ day) (Spearman r=0.42, P<0.001).	No association between toenail mercury and risk of coronary heart disease [1st (median 0.15 ppm (range 0.03–0.21) *vs.* 5th (1.34 ppm (range, 0.87–14.56) quintile RR=0.97 (95% CI, 0.63–1.50; P trend=0.78).	NOAEL >1.34 ppm toenail mercury (~3.35 ppm)	Toenail Hg significantly correlated with fish consumption. Men in the highest mercury and highest cadmium category combined had no elevated risk of CHD.
Yorifuji *et al.* (2010)	Minamata cohort	Men and women aged 10 years or	3038 subjects	Hypertension prevalence	Hair Mercury and geographic	No association between	NOAEL >28.3 ppm hair	Quartile exposure categories were <6.2, 6.2–16.2, 16.2–28.3,

		older			area. In Minamata, Goshonoura, and Kumamoto median hair mercury = 30.0 ppm, 21.5 ppm, and 2.1 ppm. Ariake estimated ~ Kumamoto. Kumamoto area not included in analysis.	hypertension and hair mercury. However, when comparing areas of high *vs*. low exposure in relation to their proximity to Minamata, there was elevated risk of hypertension prevalence with high exposure areas.	mercury	>28.3 ppm and contained 32, 28, 30, and 30 subjects, respectively. Low numbers of subjects per group and point of reference was higher than most populations' mercury exposures at 6.2 ppm in hair. It is possible that the cardiovascular response curve either plateaued or did not rise appreciably with mercury exposure beyond that exposure. No clear dose-response relationship between residential area and hypertension: the prevalence was the highest in the Minamata area (high exposure) and the lowest in the Goshonoura area (medium exposure).
Yaginuma-Sakurai *et al.* 2010	Japan intervention study to test safety of PTWI level (2005) of 3.4 μg Hg/kg bw/day	Adult men and women	14 men and 13 women in each of the control and exposed groups	Heart Rate Variability (HRV)	Baseline, 15th week, and 29th week: Hair Hg, plasma DHA+EPA, HRV. Exposure source, muscle of two big eye tuna and a swordfish (mean total Hg = 1.08	Yes.	LOAEL =8.76 ppm in hair, but could be as low as 5 ppm hair. NOAEL =3 ppm in hair, but could be as high as 5 ppm in hair.	Elevated LF and LF/HF associated with 8.76 ppm mean hair mercury *vs*. 2.30 ppm baseline and 4.9 ppm post exposure/clearance. No change in CVRR, CVHF, or HR. Not clear if these transient findings would have persisted chronically. Also, approximate doubling of hair Hg at end *vs*. baseline was associated with similar HRV

					ppm for both fish)			parameters. [maybe things would have been different ina population which is accustomed to higher levels chronically]
Guallar *et al.* (2002)	Case-control study conducted in eight European countries and Israel evaluated potential myocardial infarction (MI) risk associated with fish intake and exposure to mercury and fish oil	Adult men	684 adult men <70 years of age with a first diagnosis of myocardial infarction. 724 control men.	MI	Toenail mercury, adipose tissue DHA (control average toenail Hg = 0.25 ppm; patients, 0.29 ppm average after adjustment)	Yes. Adjusted odds ratio for highest *vs*. lowest quintile of mercury = 2.16 (95% CI, 1.09 – 4.29; P for trend=0.006).	LOAEL =0.36 ppm toenail mercury (~0.9 ppm in hair)	After adjustment for the mercury level, DHA level inversely associated with the MI risk (OR for the highest *vs*. lowest quintile = 0.59 (95% CI, 0.30 – 1.19; P for trend=0.02). Rather diverse sample of subjects. Less homogeneity that may generate uncertainties in statistics.
Xun *et al.* (2012)	Meta-analysis of 19 prospective cohorts that assessed associations between fish consumption and risk of stroke (402,127 individuals)	Adult men and women age 30–103 years	10,568 incident MI cases (Total meta-analysis population=402,127)	Stroke Incidence	Fish consumption questionnaire	No	NOAEL >5 fish meals/week	Adjusted Hazard Ratios for risk from stroke from fish consumption consistently below 1.0 and statistically significantly different for those consuming up to >5 meals/week *vs*. those who ate no fish or <1 meal/month. This inverse association was particularly strong for studies conducted in North America.

Diabetes

Table. Studies and meta-analyses that assessed the effect of mercury ingestion from fish on diabetes risk

Study	Study Type	Population	Study Dates/Follow-up length	Cohort Size	Endpoint Examined	Exposure Assessment	Risk Yes/No	Comments
He *et al* 2013	Prospective Cohort	American Adults (20–32 y)	1985–2005	3,875 (288 incident diabetes cases)	Diabetes Incidence	Baseline Toenail Mercury – 1987	Yes [Hazard Ratio = 1.65 (95% Confidence Interval, CI; 1.07–2.56) for highest (quintile median, 0.61 ppm toenail mercury) *vs*. lowest quintiles (median, 0.07 ppm toenail mercury), Ptrend = 0.02] (~1.5 ppm and 0.2 ppm hair mercury, respectively)	Same CARDIA study (Li *et al.*, 2013) found a Hazard Ratio = 0.46 (95% CI: 0.33, 0.64; P-trend < 0.01) for the highest quintile of long chain omega 3 fatty acid intake as compared with the lowest quintile. No association with fish intake.
Moon 2013	Crossectional Study	Korea NHANES. Korean adults ≥ 30y (mean age, 49.4 y)	2009–2010	3,184 cases	Diabetes Prevalence	Blood metals measurement (lead, mercury, and cadmium)	No. Neither individual nor sum of individual heavy metal concentrations in blood associated with prevalence of diabetes	Crossectional study.
Xun and He, 2012	Meta-analysis	(12 prospective cohorts)	11.4 y average (1966–2011)	438,214 (18,711 incident diabetes cases)	Diabetes Incidence	Fish consumption questionnaires	No. Relative Risk of incident diabetes was 0.99 (95% CI, 0.85–1.16) for individuals who ate fish five or more times per week	Inverse association between fish intake and diabetes incidence in Eastern but not Western countries.

							(P_{trend} = 0.80).	
Wallin *et al*, 2012	Meta-analysis	(16 prospective cohorts)		527,441 (24,082 diabetes cases)	Diabetes Incidence	Fish consumption questionnaire.	Mixed. For each incremental weekly fish serving RRs (95% CIs) of type II diabetes were 1.05 (1.02–1.09), 1.03 (0.96–1.11), and 0.98 (0.97–1.00) combining U.S., European, and Asian/Australian studies, respectively.	Adverse diabetes association with fish consumption is marginally significant, RR=1.05). For a 0.30 g daily increment in long-chain n-3 fatty acids intake, the RRs (95% CIs) were 1.17 (1.09–1.26), 0.98 (0.70–1.37), and 0.90 (0.82–0.98) when combining U.S., European, and Asian/Australian studies, respectively.

Region-specific Fish Consumption Recommendations and Fish Tissue Mercury Concentrations

Table 4. Region-specific Consumption Recommendations for Northern Pike.

Watershed (including tributaries)	**Fish Length**	**N***	**Max**	**Median**	**% > 0.4 ppm**	**% > 1.0 ppm**	Meals/month
Lower Kuskokwim River (from Aniak downstream)	>2 feet	6	1.1	0.4	33%	17%	12
	< 2 feet	31	0.79	0.35	45%	0%	12
Lower Yukon River (from Holy Cross downstream)	>2 feet	63	1.36	0.7	79%	13%	4
	< 2 feet	26	0.82	0.5	65%	0%	8
Mid-Yukon River (from Kaltag to Ruby)	>2 feet	37	1.1	0.54	70%	3%	8
	< 2 feet	21	1.1	0.48	52%	5%	8
Upper Yukon River waters (from Beaver to the Black River)	>2 feet	27	1	0.76	96%	0%	4
	< 2 feet	37	1.1	0.45	57%	5%	12
Northwest Alaska (including the Noatak, Kobuk, Selawik, and Buckland Rivers)	>2 feet	25	0.61	0.31	24%	0%	16
	< 2 feet	80	0.66	0.17	10%	0%	Unrestricted

-Calculations performed using 6 ounce meal size, and Acceptable Daily Dose of 0.56 μg/kg BW/day established by the Alaska Scientific Advisory Committee for Fish Consumption

-Calculations assume a single-species diet