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Subsistence fish consumption in rural Alaska: Using regional monitoring data to evaluate risk and bioavailability of dietary methylmercury

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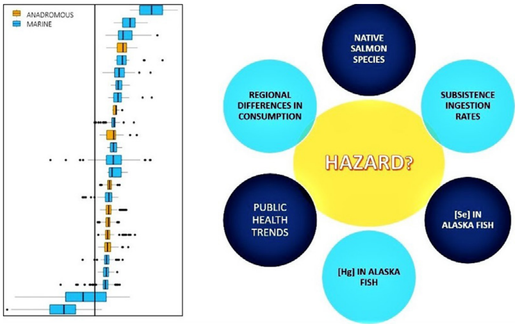
HIGHLIGHTS

- Most subsistence fish species in Alaska have relatively low methylmercury (MeHg).
- Fish from Alaska generally have positive selenium health benefit values.
- Alaskan women have low hair mercury relative to other subsistence fishing cultures.
- MeHg in salmon does not pose an unacceptable hazard for most subsistence consumers.
- Health benefits of traditional Alaskan diets may outweigh risk from MeHg exposure.

GRAPHICAL ABSTRACT



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ABSTRACT

On average, Alaskans in rural communities consume over three times the Federally recommended maximum weekly fish ingestion rate (IR), the overwhelming majority of which is Pacific salmon. Results of statewide monitoring efforts consistently show that Pacific salmon from Alaska have low concentrations of mercury, yet concerns regarding dietary exposure to methylmercury (MeHg) and other aquatic contaminants continue to contribute to declining subsistence fish consumption rates in rural communities. Therefore, the goal of the present study was to use statewide biomonitoring datasets and regional fish IRs to quantitatively evaluate potential risk from dietary MeHg exposure via subsistence consumption of salmon from Alaska. Hazard Indices (HIs) did not exceed 1 for any of the groups evaluated, indicating negligible risk for the average Alaskan subsistence consumer. Selenium health benefit values (HBV_{Se}) of various fish species from AK were also calculated, with positive results for all commonly consumed subsistence species. Additionally, mercury concentrations in the hair of Alaskan women were evaluated as a proxy for dietary MeHg exposure. Results reveal that Alaskan women of childbearing age have substantially lower hair Hg concentrations than their counterparts in other large-scale biomonitoring studies, despite similar fish IRs. Collectively, results of the present study suggest that MeHg in Pacific salmon does not pose an unacceptable hazard for the average subsistence consumer in Alaska.

1. Introduction

A wealth of scientific literature exists that describes both the health benefits and potential risks associated with regular fish consumption

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(Bernstein et al., 2019; Bramante et al., 2018; SanGiovanni and Chew, 2005; Simopoulos, 2008). Fish is a low calorie, high quality source of complete protein that contains a number of nutritional benefits, including vitamins, antioxidants, minerals and omega-3 fatty acids (Tørris et al., 2018; Uauy and Dangour, 2006). However, fish and shellfish can also accumulate potentially high body burdens of toxicants present in the aquatic environment, including methylmercury (MeHg) (Burger and Gochfeld, 2011; Drevnick et al., 2015; Wiener et al., 2012).

MeHg is a highly bioavailable and bioaccumulative form of mercury that accounts for approximately 95% of the total Hg (tHg) present in fish muscle (Depew et al., 2011; Wiener et al., 2012). It can biomagnify to levels of concern in fish, particularly in the muscle of long-lived or high trophic level species that may be consumed by humans (Barst et al., 2015; Burger and Gochfeld, 2012; Burger et al., 2012a; Drevnick et al., 2015; Sandheinrich and Wiener, 2011). Dietary exposure to MeHg can lead to profound and irreversible effects on the vertebrate nervous system, particularly when exposure occurs during development (Beyrouty et al., 2006; Bridges et al., 2017; Bridges et al., 2018; Bridges et al., 2016; Debes et al., 2016; Grandjean et al., 1997; Shao et al., 2015; Swiercz et al., 2008).

Therefore, to protect the developing nervous system against MeHg toxicity, while also maximizing the health benefits of fish consumption, the US EPA and Food and Drug Administration (FDA) jointly advise people (ages 10 and older) to consume 8 to 12-ounces, or 227 to 340-grams (g) of fish that are low in mercury per week (FDA, 2014; health.gov, 2018). These fish consumption guidelines were developed for the protection of the general US population, and are therefore primarily based on the average tHg concentrations measured in commercial sources of fish and shellfish and/or the national averages of fish caught in the contiguous US (FDA, 2014).

However, the majority of fish consumed in Alaska (AK) is locally caught Pacific salmon, which includes 5 species: Chinook, *Oncorhynchus tshawytscha*; Sockeye, *Oncorhynchus nerka*; Chum, *Oncorhynchus keta*; Coho *Oncorhynchus kisutch*; Pink, *Oncorhynchus gorbusha*. Salmon is listed among the EPA-FDA “Best Choices” category, which has a maximum recommended weekly consumption rate of 340.2-g for pregnant women and children. Nationally, the average adult fish consumer in the U.S. ingests approximately 363-g of fish per week, which is only slightly higher than the maximum recommended by the EPA-FDA for sensitive populations (USEPA, 2011). By contrast, the average Alaskan consumes anywhere from 791 to 1330-g of fish per week, with a statewide mean of 1043-g/week (Nobmann, 1991; Polissar and Neradilek, 2019).

The EPA-FDA advice has exacerbated existing concerns about the safety of fish as a subsistence resource among rural Alaskans, due to the increasing perception of fish as a contaminated resource (despite evidence to the contrary) (Arnold and Middaugh; O'Brien et al., 2017; Verbrugge, 2007). Cumulatively, these factors have contributed to a 31% decrease in the mass of subsistence food harvested per person in rural Alaska since the mid-1980s (Fall and Kostick, 2018). This trend has also been associated with a concomitant increase in certain adverse effects on public health in subsistence communities, including increased incidences of diseases of poor nutrition (e.g., diabetes, obesity, and cardiovascular disease) and declines in mental health (Arnold and Middaugh; Ebbesson et al., 1999; Fall et al., 2019; Fall and Kostick, 2018; Kuhnlein, 2015).,

Therefore, the goal of the present study is to use up-to-date regional-level fish contaminant data and regionally relevant subsistence fish ingestion rates (IRs) to quantitatively evaluate the potential risk that dietary MeHg exposure may pose to Alaskans who rely on salmon as a primary subsistence resource. Results of the quantitative risk assessment are also augmented by additional lines of evidence to reduce uncertainty, which include an evaluation of the selenium health benefit values (HBV_{Se}) of common fish species from Alaska, as well as results of a statewide hair mercury biomonitoring program.

2. Methods

This evaluation relies on data collected as part of statewide biomonitoring programs performed by the Office of the State Veterinarian (within the AK Department of Environmental Conservation) and the Environmental Public Health Program (within the AK Division of Public Health), as well as previously published subsistence harvest data provided by the Division of Subsistence (within the AK Department of Fish and Game; Fall et al., 2019). Original fish tissue data for tHg, MeHg, and Se concentrations in tissues of various marine and anadromous fish species were provided by the Office of the State Veterinarian (https://dec.alaska.gov/eh/vet/fish-monitoring-program/fish-tissue-mercury). The Environmental Public Health Program provided original hair Hg data collected from Alaskan women living in subsistence communities across the state.

2.1. Fish biomonitoring sample collection

The Office of the State Veterinarian Fish Monitoring Program surveys a variety of marine and freshwater fish and shellfish species from across AK in collaboration with State and Federal scientists from the Alaska Department of Fish & Game (ADF&G), the US National Oceanic and Atmospheric Administration (NOAA), the US Fish & Wildlife Service (USF&W), the International Pacific Halibut Commission (IPHC), and commercial and subsistence fishermen and women. Since its inception in 2001, the Fish Monitoring Program has analyzed over 13,000 tissue samples from 102 different species of fish and shellfish from across Alaska for a variety of environmental contaminants, including mercury. A standard operating procedure for sample collection is provided by the Office of the State Veterinarian, in the form of the Fish Monitoring Program Field Manual and Quality Assurance Project Plan for Fish Safety Monitoring (Gerlach and Furin, 2017). An overview of general methods is provided in the supplementary material.

2.2. Analytical methods for Hg and Se in fish

Homogenized, skinless fillets of individual fish were used for analysis. A DMA-80 Direct Mercury Analyzer (Milestone Inc., Shelton, CT) was used to measure [tHg], according to the methods outlined in EPA Method 7473 (USEPA, 2007). A DORM-4 Certified Reference Material (CRM; National Research Council Canada), method blank, sample duplicate, matrix spike, and matrix spike duplicate were run every 10–20 samples (depending on batch size). Results were only accepted if the following requirements were met: sample duplicate relative % deviation (RPD) $< 20\%$, spike and spike duplicate RPD $< 20\%$, and CRM $\pm$ 10% of certified value. The reporting limit for total mercury was 0.025 mg/kg and the method detection limit (MDL) was 0.0048 mg/kg. Mercury concentrations below the reporting limit were assigned a value equal to half the reporting limit (0.012 mg/kg).

Samples were prepared for Se analysis following the digestion protocols outlined in EPA Method 3051A. Prepared samples were then analyzed via inductively coupled plasma mass spectrometry (ICP-MS) using EPA method 6020. CRMs and internal standards (purchased from AccuStandard Inc. and Inorganic Ventures) were used to prepare calibration curves and spikes, which were run after every 20th sample or less (depending on batch size). Method blanks and duplicates were run with the same frequency. The following quality assurance requirements had to be met for inclusion in the dataset: sample duplicate RPD $< 20\%$, spike and spike duplicate RPD $< 20\%$, and 80–120% recovery of Internal Standard. The reporting limit was 0.05 for selenium and the MDL was 0.01 mg/kg. All analytical results are reported as mg/kg wet weight (WW).

2.3. Risk calculations for mercury in AK Salmon

Due to the overwhelming prevalence of the MeHg form in the muscle of fish, and for added conservativism, it was assumed that 100% of mercury in fish muscle was MeHg. An estimated tHg exposure dose (D; mg/kg/day) was derived for an Alaskan adult consuming salmon as a subsistence resource, using the formula $D = (C \times IR \times EF) / BW$; where, C is the median [tHg] measured in the fillets of each species of Pacific salmon from AK, BW is body weight (kg), and ingestion rate (IR) is a regionally-specific ingestion rate (kg/day) for each species of salmon (published by the ADF&G Division of Subsistence; Fall et al., 2019) over a given exposure duration and frequency (EF) (ATSDR, 2005). The value for D was then compared to the RfD for MeHg (0.0001 mg/kg/day) provided by the US EPA, to yield a Hazard Quotient (HQ) (ATSDR, 2005). In exposure scenarios where the $HQ > 1$, a potential increase in the risk of developing adverse (non-cancerous) health effects from exposure to a toxic substance exists, whereas a $HQ < 1$ indicates negligible risk to health (ATSDR, 2005). In instances where there is concurrent exposure to multiple hazards, or exposure from multiple sources (i.e., exposure to tHg from consumption of multiple fish species), the sum of individual HQs, or Hazard Index (HI), yields an overall estimate of hazard (ATSDR, 2005). All exposure factor values used in calculations were provided by the US EPA Exposure Factors Handbook (EFH) and/or the Agency for Toxic Substances and Disease Registry (ATSDR, 2005), unless otherwise stated.

2.4. Selenium health benefit values (HBV_{Se})

To provide an additional line of evidence in support of our risk calculations (that consider only Hg content in fish muscle), we also calculated a HBV_{Se} for a number of fish species. Because of the potential for large individual variation of contaminant concentrations, species and/or tissues with <15 samples were excluded from our analysis. Additionally, due to differences in life history strategies, habitat use, limited consumption on a statewide level, and geographical differences in the naturally occurring mineral composition of soil/sediments from various regions in AK, we concluded that a separate evaluation for freshwater fish species was more appropriate. Therefore, the present study only includes data from anadromous fish, marine fish, and marine invertebrates with sufficient sample sizes. After filtering the dataset to meet inclusion requirements, results from 6303 tissue samples from all six regions across the state (Fig. 1A) remained, representing 29 species of fish and shellfish native to AK.

For each species of fish and invertebrate included in the dataset, an HBV_{Se} was calculated, using the following equation developed by Ralston et al. (2016):

$$\mathrm{HBV_{Se}} = ([\mathrm{Se} - \mathrm{tHg}]/\mathrm{Se}) \times (\mathrm{Se} + \mathrm{tHg})$$

where;

HBV_{Se} is the selenium health benefit value
Se is the concentration of selenium in fish muscle
tHg is the concentration of total mercury in fish muscle.

The HBV_{Se}, approach is based on the premise that dietary co-exposure to equimolar (or greater) ratios of Se:Hg is expected to ameliorate the neurotoxic effects associated with Hg exposure.

2.5. Hair mercury biomonitoring data collection

In July 2002, the Environmental Public Health Program initiated its Statewide Maternal Hair Mercury Biomonitoring Program to monitor the hair mercury concentrations of women in Alaska. Hair samples were collected by either health care providers, or participants themselves, using a standardized collection method provided by the Environmental Public Health Program (described in the accompanying SI file). Samples submitted between July 2002 and September 2017 were included in the present study, yielding a total of 1779 samples from women in 168 communities in Alaska.

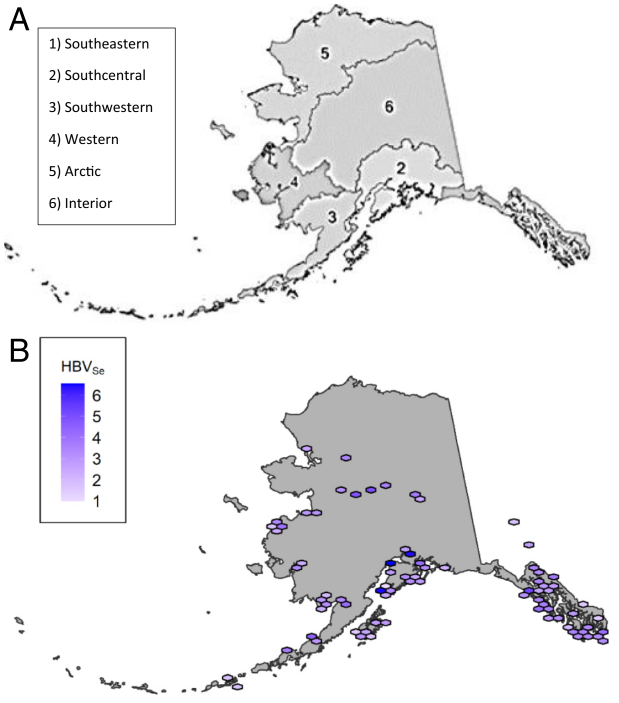

Fig. 1. A) Regional boundaries for the six resource conservation areas in Alaska (figure adapted from the Alaska Department of Fish & Game 2019 Regulatory Atlas Map). B) Shaded hexagons denote sampling locations and HBV_{Se} values of Pacific salmon analyzed as part of the present study.

3. Results and discussion

3.1. Fish consumption trends in Alaska

Data published by the ADF&G Division of Subsistence indicates that fish accounts for approximately 53% of the usable wild food mass harvested by subsistence users in AK (shellfish contribute an additional 3% to food mass) (Fall et al., 2019). Harvest surveys conducted in rural and Alaska Native communities report regional differences (Arctic, Interior, Southcentral, Southeast, Southwest, Western; Fig. 1A) in mean daily fish consumption rates for adults, ranging from approximately 113-g/day in Southcentral AK to 190-g/day in the Western region of the state (Polissar and Neradilek, 2019). The 90th percentile consumption rates reported for adults also varied regionally, with values ranging from 217-g/day in Southcentral to 379-g/day in Western AK (Polissar and Neradilek, 2019). When consumption of all five salmon species are considered together, ADF&G estimates that salmon accounts for a minimum of 43% of total fish consumption (Arctic), up to a maximum of 95% of fish consumption (Southwest) in AK.

There are also regional differences in the dietary contribution made by each of the native salmon species, with Chinook and Sockeye salmon generally exhibiting the largest consumption rates in all regions, except in the Arctic, where Chum salmon is consumed with the highest frequency (Table 1) (Fall et al., 2019; Fall and Kostick, 2018). However, consumption of these resources is steadily declining in all regions, driven in large part by concerns over environmental contamination, especially MeHg (Arnold and Middaugh; Ebbesson et al., 1999; Kuhnlein, 2015). This perception exists despite the low contaminant levels measured in the fish species most commonly consumed in AK (salmon,

Table 1
Regionally adjusted risk estimates for adult Alaskans exposed to dietary MeHg through subsistence consumption of salmon, presented as a Hazard Quotient (HQ) and Hazard Index (HI).

Region	Salmon species	tHg (mg/kg)	% of all fish consumed[a]	IR[a] (g/day)	BW (kg)	Dose (mg/kg/day)	HQ[b]
Arctic	Chinook	0.06	1%	1.2	80	9.00E−07	0.0
	Chum	0.04	31%	41.6		2.08E−05	0.2
	Coho	0.04	7%	9.7		4.85E−06	0.0
	Pink	0.01	3%	3.7		4.63E−07	0.0
	Sockeye	0.04	2%	2.3		1.15E−06	0.0
	Totals		43%	58.5		**HI**	0.3
Interior	Chinook	0.06	29%	32.2	80	2.42E−05	0.2
	Chum	0.04	17%	18.8		9.40E−06	0.1
	Coho	0.04	15%	17		8.50E−06	0.1
	Pink	0.01	1%	0.7		8.75E−08	0.0
	Sockeye	0.04	8%	8.8		4.40E−06	0.0
	Totals		70%	77.5		**HI**	0.5
Southcentral	Chinook	0.06	12%	14.1	80	1.06E−05	0.1
	Chum	0.04	2%	1.9		9.50E−07	0.0
	Coho	0.04	12%	14.3		7.15E−06	0.1
	Pink	0.01	4%	4.6		5.75E−07	0.0
	Sockeye	0.04	48%	55.4		2.77E−05	0.3
	Totals		79%	90.3		**HI**	0.5
Southeast	Chinook	0.06	9%	13.7	80	1.03E−05	0.1
	Chum	0.04	3%	5.1		2.55E−06	0.0
	Coho	0.04	16%	23.6		1.18E−05	0.1
	Pink	0.01	3%	4.8		6.00E−07	0.0
	Sockeye	0.04	32%	46.9		2.35E−05	0.2
	Totals		64%	94.1		**HI**	0.5
Southwest	Chinook	0.06	36%	65.1	80	4.88E−05	0.5
	Chum	0.04	8%	14		7.00E−06	0.1
	Coho	0.04	19%	34.3		1.72E−05	0.2
	Pink	0.01	3%	5.7		7.13E−07	0.0
	Sockeye	0.04	30%	54.3		2.72E−05	0.3
	Totals		95%	173.4		**HI**	1.0
Western	Chinook	0.06	19%	38.7	80	2.90E−05	0.3
	Chum	0.04	25%	49.2		2.46E−05	0.2
	Coho	0.04	11%	21.3		1.07E−05	0.1
	Pink	0.01	1%	1.3		1.63E−07	0.0
	Sockeye	0.04	10%	19.9		9.95E−06	0.1
	Totals		65%	130.4		**HI**	0.7

[a] Reported by the Alaska Department of Fish & Game Division of Subsistence (Fall 2018; Fall et al., 2019; Polissar and Neradilek, 2019).
[b] HQ or HI > 1 indicates potential risk related to MeHg exposure (using a chronic oral RfD of 0.0001 mg/kg/day).

followed by certain size-classes of halibut) in this, and other studies (Arnold et al., 2005; Ballew et al., 2006).

3.2. Mercury in fish from Alaska

Concentrations of tHg in samples (Table S1) selected for inclusion in the present study ranged from 0.012 to a maximum of 2.07-mg/kg WW in salmon shark. Salmon shark was also the only species included in the present analysis to have a mean or median tHg concentration in muscle that exceeded the FDA action level of 1-mg/kg WW; however, there were some individual fish from seven other species (spiny dogfish, Pacific halibut, yelloweye rockfish, lingcod, quillback rockfish, sablefish, and longnose skate fillets) that had concentrations of Hg in muscle that met or exceeded the FDA action level (FDA, 2014; health.gov, 2018). Maximum detected mercury concentrations for all other species were well below the action level (Table S1), although there was considerable variation within some species, underscoring the importance of sufficient sample sizes in analyses of this kind.

All five species of Pacific salmon had relatively low median [tHg] (Chinook, 0.06; Coho, 0.04; Pink, 0.01; Sockeye, 0.04; Chum, 0.04-mg/kg WW) (Fig. 2; Table S1). The median [tHg] for all five species of salmon caught in AK were similar to those measured elsewhere along the U.S. Pacific coast (Table S2), with the exception of Sockeye salmon from Oregon (OR), which had elevated values relative to fish from AK, WA, BC, and California (Chinook salmon from WA also appeared to be slightly elevated relative to AK) (Kelly et al., 2008). Wild caught Atlantic salmon from the East coast of the US also had higher mean tHg in fillets (mean WW concentrations ranged from 0.12 [converted from dry weight in Jardine et al., 2009] to 0.17-mg/kg WW (USEPA)) than Pacific salmon from AK (Table S2). All species of farmed salmon (Atlantic, Coho and Chinook) had low tHg (0.02 to 0.03-mg/kg WW; Table S2 (Jardine et al., 2009; Karimi et al., 2012; Kelly et al., 2008; USEPA)), with concentrations similar to those measured in Chum, Coho, Pink, and Sockeye salmon in AK. It is worth noting that multiple studies have determined that mercury exposure from Atlantic salmon (the majority of which is farmed) is not a significant human health concern (Dewailly et al., 2007; Jardine et al., 2009; Kelly et al., 2008).

3.3. Evaluation of mercury exposure and risk

Regionally specific consumption rates for all five species of Pacific salmon from AK were used to calculate mercury exposure estimates for subsistence consumers in Alaska. Results suggest that current salmon consumption rates are not exposing the average subsistence consumer in AK to doses of mercury that exceed the EPA Chronic Exposure Reference Dose for MeHg (0.0001 mg/kg/day), despite exceeding the EPA-FDA consumption recommendations several times over (ATSDR, 2005; FDA, 2014; health.gov, 2018; Polissar and Neradilek, 2019). This is demonstrated by the HQ/HI values for adult subsistence users, which do not exceed 1 in any region (Table 1). However, in Southwest Alaska, where salmon accounts for 95% of all fish consumption, the HI = 1. An HI = 1 (or >1 in some cases) does not necessarily indicate that adverse health outcomes are expected; however, it does indicate that the potential for health effects exists and that further toxicological evaluation is needed (ATSDR, 2005; USEPA, 1989; USEPA, 2000). It is important to note the limitations of the HQ/HI values reported in

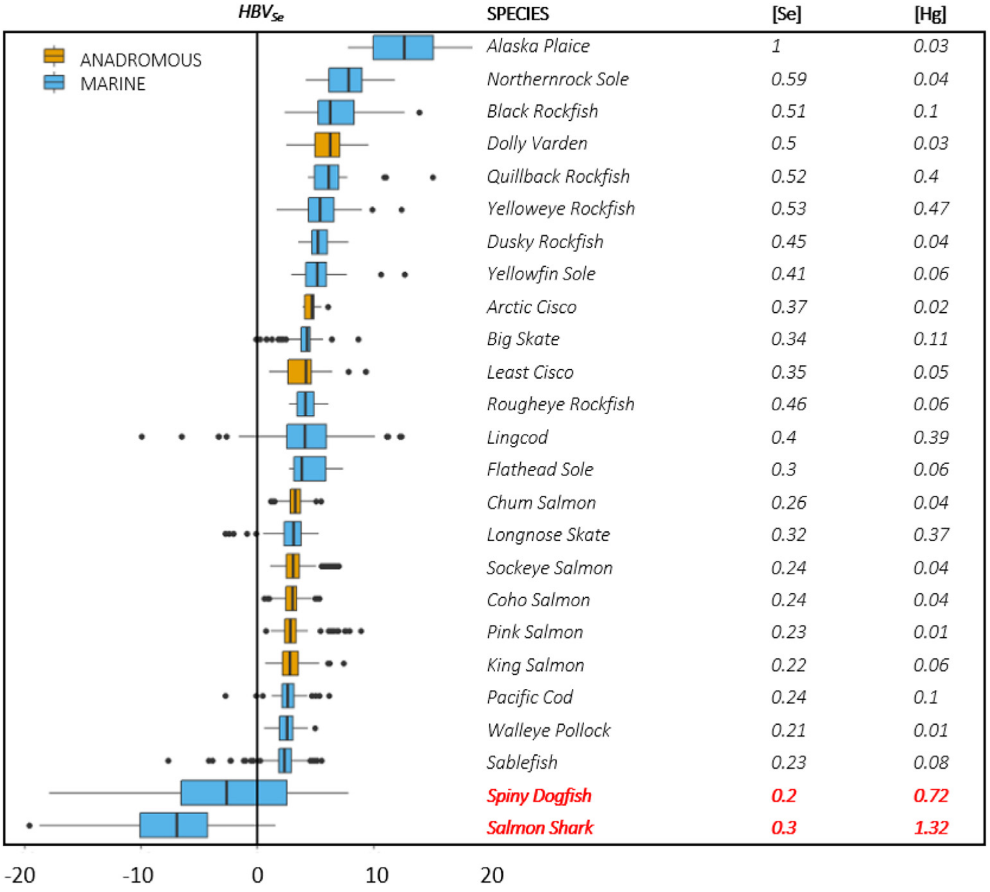

Fig. 2. Selenium [Se], total mercury [Hg], and selenium health benefit values (HBV_{Se}) measured in the skinless fillets of select anadromous and marine fish species from Alaska (all concentrations are reported as mg/kg WW; see Table S1 for additional data).

Table 1, which do not account for 95th percentile adult consumers, consumption of other fish species, consumption of marine mammal organs, or interactions between Hg and Se that may modulate toxicity. Additionally, the EPA RfD for MeHg (that was used to calculate hazard quotients) is designed to be protective of pregnant women and developing fetuses; however, there is uncertainty surrounding the relevance of these hazard estimates to other life stages (i.e., young children), as ADF&G did not publish their data in a format that identified ingestion rates by age class.

Fish consumption advice is especially important for young children, as it is widely accepted that the developing nervous system is more sensitive to the toxic effects of MeHg (Grandjean and Landrigan, 2014; Grandjean et al., 2010; Grandjean et al., 1999). The EPA's Exposure Factors Handbook (USEPA, 2011) does not provide reliable fish and shellfish ingestion rates for indigenous children in the US and Canada. This data gap both complicates exposure and hazard evaluations for American Indian and Alaska Native children and makes comparisons between studies difficult, due to a lack of standardized reporting methods.

Because Alaska Natives tend to have some of the highest fish consumption rates in North America (Polissar and Neradilek, 2019), we opted to calculate a threshold ingestion rate (g/day) for children consuming each species of salmon in lieu of an HQ. The threshold ingestion rate represents the consumption rate above which the average child from a given age class would be expected to exceed the chronic oral RfD for MeHg (Table 2). Threshold ingestion rate values for Chinook salmon, which have a slightly higher body burden of Hg than the other four species of Pacific salmon, ranged from 19.0-g/day for a 1-year old child (or 4.7-oz/week), to 119.3-g/day for children ≥ 16-years old (or 29.5-oz/week; Table 2). Coho, chum, sockeye, and pink salmon

Table 2
Species-specific salmon threshold ingestion rate (g/day), above which the average Alaskan child from each age class is expected to exceed the US EPA RfD and Alaska ADI, as compared with HBV_{Se} findings.

Age (years)	BW (kg)	Salmon species	[tHg] (mg/kg)	Threshold IR (g/day) - EPA RfD[a]	Threshold IR (g/day) - AK ADI[b]	Threshold IR (g/day) - *HBVSe*
1 < 2	11.4	Chinook	0.06	19.0	106.4	Unrestricted
		Chum	0.04	28.5	159.6	
		Coho	0.04	28.5	159.6	
		Pink	0.01	114	638.4	
		Sockeye	0.04	28.5	159.6	
2 < 6	17.4	Chinook	0.06	29.0	162.4	Unrestricted
		Chum	0.04	43.5	243.6	
		Coho	0.04	43.5	243.6	
		Pink	0.01	43.5	974.4	
		Sockeye	0.04	43.5	243.6	
6 < 11	31.8	Chinook	0.06	53.0	296.8	Unrestricted
		Chum	0.04	79.5	445.2	
		Coho	0.04	79.5	445.2	
		Pink	0.01	79.5	1780.8	
		Sockeye	0.04	79.5	445.2	
11 < 16	56.8	Chinook	0.06	94.7	530.1	Unrestricted
		Chum	0.04	142	795.2	
		Coho	0.04	142	795.2	
		Pink	0.01	142	3180.8	
		Sockeye	0.04	142	795.2	
16 < 21	71.6	Chinook	0.06	119.3	668.3	Unrestricted
		Chum	0.04	179	1002.4	
		Coho	0.04	179	1002.4	
		Pink	0.01	179	4009.6	
		Sockeye	0.04	179	1002.4	

[a] EPA RfD for chronic oral exposure to dietary MeHg = 0.0001 mg/kg/day.
[b] Alaska ADI for chronic oral exposure to dietary MeHg = 0.00056 mg/kg/day.

had threshold ingestion rate values ranging from 28.5-g/day for 1-year old children (7-oz/week), to 179-g/day for children ≥ 16-years old (44.2-oz/week; Table 2). As previously mentioned,

The limited amount of fish ingestion data available for Native American children (from tribes that consume fish as a subsistence resource) suggests that 1 to 2-year old children may ingest fish at a rate between 10-g/day (in the Mohawk Tribe in New York and Eastern Canada) to approximately 33 g/day in the Squaxin Island Tribe (in Washington state) (USEPA, 2011). However, it is important to note that the upper bound estimate (i.e., the ingestion rate reported for children from the Squaxin Island tribe) may be biased toward added conservatism for 1 to 2-year old children, as the ingestion rate for that study was derived using data from children as old as 5. Nevertheless, when the Squaxin Island ingestion rate is used as an exposure parameter for children 2-years and younger, it appears that concentrations of Hg in Coho, Sockeye, Pink, and Chum salmon from AK may lead to exposure in excess of the EPA's RfD for MeHg in subsistence communities, while children ages 2 to 6 may exceed the RfD for MeHg when consuming Chinook salmon as a subsistence resource.

3.4. Additional lines of evidence

Due to the potency of MeHg as a neurotoxicant and the severity and permanence of potential effects, we sought other lines of evidence in an effort to address the aforementioned uncertainties surrounding risk calculations (i.e., 95th percentile consumers, other source contributions, and sensitive life stages). It has been suggested that inhibition of selenium (Se) dependent enzymes (selenoenzymes) by MeHg (which irreversibly binds Se) may be the primary mechanism of action by which MeHg leads to developmental neurotoxicity (Ralston et al., 2012; Ralston et al., 2019; Ralston et al., 2016; Ralston and Raymond, 2010). Because of the important interactions between Se and Hg that influence toxicity, some risk assessors argue that the molar ratios of Se:Hg in fish muscle should be taken into consideration when evaluating risk (Azad et al., 2019; Burger and Gochfeld, 2012; Burger et al., 2012a; Burger et al., 2013; Burger et al., 2011; Cusack et al., 2017; Ralston et al., 2012; Ralston et al., 2019; Ralston et al., 2016; Ralston and Raymond, 2010). However, the wide inter- and intra-species variation in Se:Hg molar ratios found in fish (due to location, age, trophic position, habitat use, wild caught vs. cultured, life-history strategy, point sources of pollution, etc.) diminishes the usefulness of these ratios to Federal-level regulators tasked with developing national fish consumption guidelines (Burger and Gochfeld, 2011; Burger and Gochfeld, 2012; Burger et al., 2012a; Burger et al., 2012b; Burger et al., 2011). Consequently, the EPA and FDA do not consider co-exposure to dietary Se in the derivation of risk-based fish consumption guidelines for MeHg (FDA, 2014; health.gov, 2018).

To supplement our hazard evaluation, we calculated the HBV_{Se} for a number of marine and anadromous fish species in AK, using Hg and Se data collected by the State Fish Monitoring Program. The HBV_{Se} was designed as a tool to consider the risk posed by concurrent dietary exposure to Hg and Se during pregnancy and early development (Ralston et al., 2016). Results revealed positive mean and median HBV_{Se} values for all species of fish and shellfish from AK, with the exception of two shark species (Fig. 2; Table S3). This is unsurprising, given that long-lived apex predators can accumulate very high body burdens of dietary MeHg through biomagnification (Kaneko and Ralston, 2007; Ralston et al., 2019; Wiener et al., 2012; Wiener and Spry, 1996). Fortunately, fish from the Elasmobranchii subclass, which includes both shark and dogfish, are not commonly consumed and not considered a subsistence resource in AK (Arnold and Middaugh; Ballew et al., 2006; Merrill and Opheim, 2013). The median HBV_{Se} was positive for all five species of salmon, regardless of the region of origin (Fig. 1B). The median HBV_{Se} was also relatively similar between species (Chinook, 2.77; Coho, 2.99; Pink, 2.84; Sockeye, 3.08; and Chum, 3.3; Fig. 2, Table S3).

Additionally, we evaluated hair mercury concentrations of Alaskan women (n = 1779) from 168 communities statewide, as a proxy for human dietary MeHg exposure. Hair mercury data can provide valuable information regarding individual exposure due to the dominance (80%) of MeHg over other the inorganic or elemental forms in hair, the non-invasive nature of the sampling method, and the demonstrated correlation with dietary MeHg intake (Freire et al., 2010; Kusanagi et al., 2018; McDowell et al., 2004). The demographic targeted by the Hair Mercury Biomonitoring Program was women of childbearing age (ages 16–49); however, the ages of female participants in the program ranged from 6 to 95-years old, with the following composition: 0.7% (n = 13) of participants were between 0 and 15-years old, 59.7% (n = 1062) of participants were between ages 16 and 49, and 39.6% (n = 704) of participants were 50 to 95-years old.

Hair samples with detectible levels of Hg ranged 0.012 to 10.6-mg/kg (in a 67-year old female). After filtering the dataset to include only women of childbearing age, the geometric mean (±standard error) hair mercury concentration of study participants was 0.39 ± 0.02 mg/kg (Fig. 3A). Nationally, the mean hair mercury concentration for this demographic (i.e., women of childbearing age that are frequent fish consumers) was strikingly similar, at 0.38-mg/kg (n = 447; Fig. 3B) (McDowell et al., 2004). According to the EPA (USEPA, 2011), the 95th percentile fish and shellfish consumption rate among women of childbearing age in the U.S. is 596.4 g/week (wet weight; n = 2332). Assuming this ingestion rate adequately represents the frequent fish consumer category, it would appear that Alaskan women consume 43% more fish on average than their counterparts in from the nationwide hair mercury study, with nearly identical mean hair mercury concentrations.

Several other studies report hair [tHg] in women from various global regions where fish is consumed as a primary protein source, all of which show considerably higher mean concentrations than those in our biomonitoring dataset (Fig. 3B; Table 3) (Cernichiari et al., 1995; Davidson et al., 1998; Freire et al., 2010; Grandjean et al., 1992; Stern et al., 2001; Yasutake et al., 2003; Yusà et al., 2017; Zhang et al., 2009). For example, mean hair [tHg] in Grenadi women was 1.2 mg/kg (Freire et al., 2010; Yusà et al., 2017), women from Japan had means ranging from 1.43–1.83 mg/kg in two separate studies (Yasutake et al., 2003; Zhang et al., 2009), and Cambodian women from Kien Svey had a mean of 5.1 mg/kg tHg (Agusa et al., 2005). Multiple mechanisms could explain these differences (e.g., fish species availability and/or preferences, consumption of marine mammals, etc.; Table 3); however, some studies provide evidence to suggest the formation of insoluble Hg-Se complexes affects the range of mean hair [tHg] observed in females from different subsistence communities (Passos et al., 2003; Ralston et al., 2012; Ralston et al., 2016; Ralston and Raymond, 2010; Wang and Gao, 2001).

Two of the most well-studied subsistence fishing communities, with respect to effects of dietary MeHg exposure, are those in the Seychelles and the Faroe Islands, both of which have fish consumption rates that are similar to those of AK women (e.g., women in the Seychelles have an estimated ingestion rate of up to 1356-g/week as compared with AK women, who consume up to 1330-g/week; Table 3). Despite similar intake rates, the mean hair mercury concentrations in women of childbearing age from all three locations differ significantly, with a mean of 4.5-mg/kg Hg in Faroese women (Yasutake et al., 2003), 6.85-mg/kg Hg in women from the Seychelles (Cernichiari et al., 1995; Grandjean et al., 1992) and 0.39-mg/kg in women from AK (Fig. 3B; Table 3).

In addition to finding differences in mean hair Hg concentrations by location, large-scale studies conducted in the Faroe Islands and the Seychelles also reached different conclusions regarding the manifestation of neurotoxicity in children exposed to maternally-derived dietary MeHg. No effects were observed in the Seychelles study, while effects of prenatal MeHg exposure in Faroese children were significant enough to allow for the derivation of a no observed adverse effect level (NOAEL) for developmental neurotoxicity (NOAEL = 10 mg/kg Hg). Twelve percent of the Faroese study participants had hair Hg concentrations that

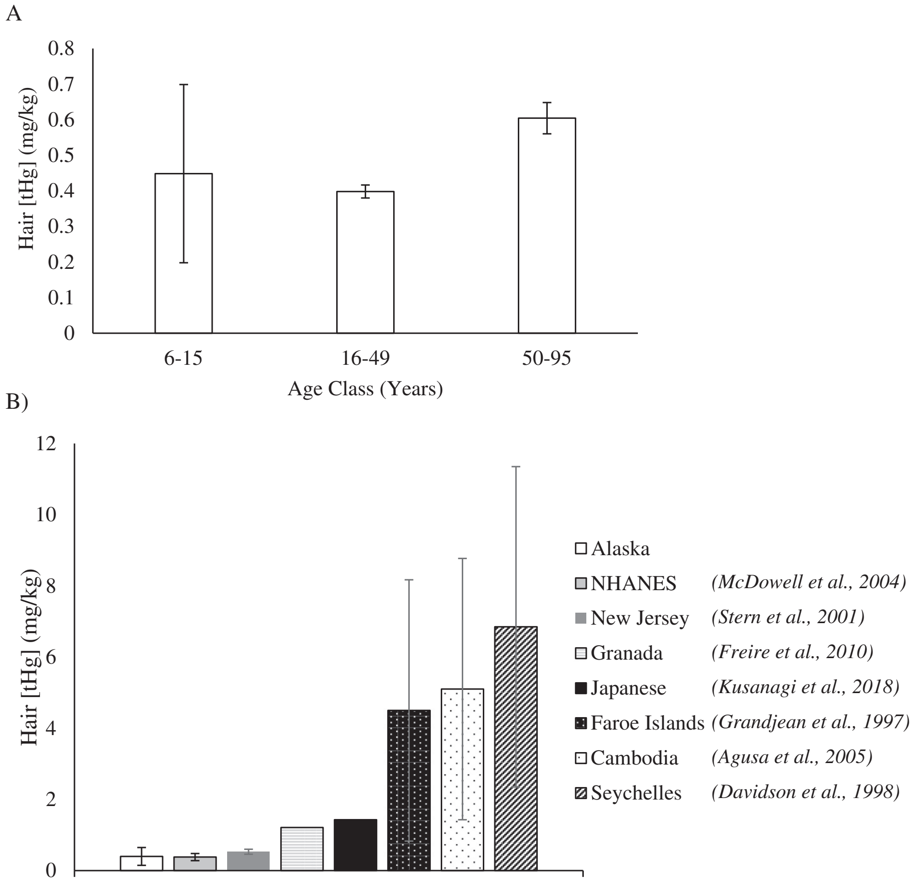

Fig. 3. Mean hair total Hg (mg/kg) values measured in A) a total of 1, 779 women from Alaska, broken down by age class (n = 13 for ages 6–15, n = 1062 for 16–49, and n = 704 for ages 50–95), and B) women of childbearing age in Alaska, as compared with those from females in other regions with heavy fish consumption rates (error bars represent ±1 SE, where available).

exceeded the NOAEL of 10 mg/kg, which may be attributed to pilot whale consumption (Grandjean et al., 1997; Grandjean et al., 1999; Ralston et al., 2019). HBV_{Se} values reported in the literature for pilot whales range from −18.6 to −82.3, indicating that Se as a micronutrient may be substantially depleted by MeHg present in molar excess during fetal development (Ralston et al., 2016). These results may provide an additional link between the HBV_{Se} of common subsistence species, the concentrations of Hg in maternal hair, and the manifestation of neurotoxic outcomes in offspring.

The maximum hair mercury concentration observed in the biomonitoring data was from a 67-year old female study participant from Southwest AK (Fig. 1A), who had a hair mercury concentration of 10.6-mg/kg (just above the 10 mg/kg NOAEL for developmental toxicity, Grandjean et al., 1992). Including this individual, a total of 16 women (approximately 0.9% of the sample population) had concentrations of mercury in their hair ≥5.0-mg/kg, all of whom were from Southwest AK (Fig. 1A). Fifteen of those women were beyond their childbearing years, though one 41-year old individual had a hair mercury concentration of 6.4-mg/kg. Marine mammal consumption in Southwest AK, particularly in the Aleutian Islands, has previously been linked to above average (for Alaskan women) hair mercury concentrations (Arnold et al., 2005; Verbrugge, 2007). Accordingly, results of individual

Table 3
Summary of fish ingestion rates, preferred subsistence fish species, marine mammal consumption habits, and mean/median hair mercury concentrations measured in women of childbearing age, for various study populations.

Study location	Fish ingestion rates (g/week)	Mean/median hair Hg (mg/kg)	Primary fish species consumed	Consume marine mammals	Reference(s)
Alaska	1043 (statewide) 791–1330 (regionally)	0.39	Pacific salmon (all 5 species)	Regionally	Present study; Polissar and Neradilek, 2019
Seychelles	1356[a]	6.85	Unspecified ocean fish	No	Cernichiari et al., 1995; Grandjean et al., 1992
Faroe Islands	504	4.5	Cod	Yes	Grandjean et al., 1992
NHANES	596[b]	0.38	Unspecified	No	McDowell et al., 2004; USEPA, 2011
Japan	616	1.43–1.83	Tuna, seabream, flounder	No	Yasutake et al., 2003; Zhang et al., 2009
Granada	546–731	1.22	Unspecified	No	Freire et al., 2010; Ramon et al. 2011; Yusà et al., 2017
Cambodia	228	5.1	Unspecified	No	Agusa et al., 2005

[a] Assuming each serving is approximately 170-g (6-oz).

[b] Fish consumption rate for women of childbearing age that were classified as “frequent fish consumers” by the NHANES study was estimated to be equivalent to the 95th percentile fish and shellfish consumption rate (among consumers only) reported in the USEPA Exposure Factors Handbook (USEPA, 2011).

follow-up consultations with those 16 study participants generally confirmed consumption of marine mammal tissues, including organs that have the potential to contain Hg in molar excess of Se (e.g., liver, kidney) (Bełdowska and Falkowska, 2016; Hoguet et al., 2013; Marino et al., 2011).

When the aforementioned study findings are taken together, it appears reasonable to suggest that the selenium and mercury molar ratios of fish commonly consumed by women in subsistence communities may contribute to differences in hair Hg, at similar ingestion rates. Results of the HBV_{Se} analysis provide an additional line of evidence in support of the findings of our risk calculations for salmon (which target the average adult subsistence consumer), while also potentially reducing uncertainty associated with upper bound subsistence consumption rates, additional source contributions (as nearly all important subsistence fish species have positive HBV_{Se} values), and sensitive life stages (Ikemoto et al., 2004; Mulder et al., 2012; Ralston et al., 2012; Ralston et al., 2016; Ralston and Raymond, 2010).

3.5. Public health trends and challenges in rural Alaska

Abandoning traditional foods in favor of a western diet due to perceived or actual environmental contamination is a well-documented phenomenon in subsistence communities in North America (Arnold and Middaugh; Ebbesson et al., 1999; Kuhnlein, 2015). Similarly, several Alaska-specific studies have linked declining subsistence practices to the emergence of concerning public health trends in rural communities (Arnold and Middaugh; Bersamin et al., 2007; Ebbesson et al., 1999; Luick et al., 2014; Mohatt et al., 2007; Moses et al., 2009; Verbrugge, 2007; Woelber and Hull-Jilly, 2013). This is largely attributed to a combination of increased dependence on nutritionally-deficient processed foods (in lieu of wild-caught foods) and a decline in social interaction and physical activity (Arnold and Middaugh; Arnold et al., 2005; Ballew et al., 2006; Ebbesson et al., 1999; Nobmann, 1991). Consequently, an increase in the incidence of diseases related to poor dietary choices (e.g., diabetes, obesity, and cardiovascular disease) has been observed among Alaska Natives (Arnold and Middaugh; Arnold et al., 2005; Bersamin et al., 2007; Ebbesson et al., 1999; Mohatt et al., 2007), including a 110% increase in the incidence of diabetes among teenagers (ages 15–19).

Childhood rickets (caused by vitamin D3 deficiency from insufficient dermal exposure to ultraviolet radiation) is another public health concern in Alaska that is increasing in prevalence, particularly among Alaska Native children (Arnold and Middaugh; Luick et al., 2014; Rajakumar et al., 2007). This too, is partially attributed to declining subsistence rates, as many subsistence foods (e.g., herring, and salmon, oysters, mussels, and marine mammals) are an important dietary source of vitamin D3 (Gessner et al., 2003; Luick et al., 2014; O'Brien et al., 2017; Ross et al., 2011). Wild caught fatty fish also helps maintain optimum lipid profiles, which has been shown to have important mental health implications (Edwards et al., 1998; Grosso et al., 2014; Sublette et al., 2006). For example, low DHA levels and elevated omega-6: omega-3 fatty acid ratios (common in Western societies) correspond with an increase in depressive disorders, suicidal behaviors, and inflammatory diseases (Edwards et al., 1998; Grosso et al., 2014; Sublette et al., 2006). Collectively, the epidemiological evidence appears to suggest that traditional diets in rural Alaska confer a number of benefits and help ameliorate or minimize risk factors associated with a number of potentially serious adverse health outcomes in rural Alaska communities.

3.6. Risks in perspective and study limitations

Subsistence fishing provides a significant proportion of annual food supplies in rural Alaska and is therefore linked to a number of public health outcomes (e.g., nutrition, food security, mental health, cultural and spiritual well-being). Here, we provide an updated analysis of the potential risks associated with MeHg exposure from subsistence fishing practices in rural Alaska, using robust, regionally relevant datasets. Multiple lines of evidence collectively suggest that subsistence consumption of salmon (given current ingestion rates and Hg concentrations) is unlikely to result in MeHg exposure at levels of concern for the average subsistence consumer (i.e., chronic oral MeHg exposure $\ngtr$ 0.0001 mg/kg/day (USEPA, 2019); maternal hair Hg $\ngtr$ 10 mg/kg (Grandjean et al., 1992)). Although there appears to be negligible hazard associated with subsistence consumption of locally sourced salmon for the average Alaskan, there are a number of documented negative effects on public health associated with discontinuing traditional dietary subsistence practices.

It is important to note that there is an inherent degree of uncertainty in any risk assessment, including the present study. Factors used in risk calculations that were not previously identified include the use of exposure parameters derived from nationwide surveys (e.g., body weight at each age) for culturally and geographically distinct populations, the use of whole-dataset median Hg and Se concentrations (i.e., they are not regionally-distinct), the potential for sampling bias/contamination (due to fish monitoring program's reliance on volunteers), and the potential for concurrent exposure to other contaminants in fish muscle. There are also limitations when using the HBV_{Se} as an indicator of risk for humans, as studies investigating the interactions between Se and MeHg overwhelmingly involve non-human models (thus, the exact molar ratio at which Se prevents MeHg toxicity in humans is unknown) and the complex interactions between Se and MeHg are not yet fully understood. Finally, it is important to reiterate that the findings of the present study are specific to subsistence communities in Alaska. Although the approach presented herein may serve as a useful model for performing targeted risk assessments elsewhere, our specific findings should not be extrapolated to communities outside of Alaska without a similar analysis of large, geographically relevant datasets.

Notes

The Statewide Mercury Hair Biomonitoring Program was reviewed by the institutional review board of the Alaska Native Medical Center and was determined to be public health practice.

CRediT authorship contribution statement

Kristin N. Bridges: Conceptualization, Methodology, Formal analysis, Investigation, Visualization, Supervision, Project administration, Writing - original draft, Writing - review & editing. **Christoff G. Furin:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Visualization, Writing - review & editing. **Robert F. Gerlach:** Investigation, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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