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Mercury, selenium and arsenic concentrations in Canadian freshwater fish and a perspective on human consumption intake and risk

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Classification : Protected A

Highlights:

- Fish Hg, Se, and As concentrations differed among perturbations and ecozones.
- Fish [Hg] were the highest, and Se/Hg ratios were the lowest in reservoirs.
- Fish length at thresholds were similar for the Hg, Se/Hg, (Se-iAs)/Hg) thresholds.
- Canadians seems to intake enough Se daily to bind iAs plus Hg from fish.

Graphical abstract

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Abstract

Mercury (Hg) and arsenic (As) contamination of fish can be toxic and limit safe human consumption, whereas selenium (Se) can potentially protect fish and consumers from the adverse effects of Hg and As. We assembled datasets of the above-mentioned elements in Canadian freshwater fish and compare them with risk assessment thresholds. We further assessed linkages between the elemental concentrations and anthropogenic activities and ecozones. Mercury concentrations exceeded the retail fish Canadian threshold (0.5 µg/g wet weight) in 31% of all Walleye; this proportion rose to 64% in reservoirs. Reservoirs and lakes impacted by logging and urbanization had higher fish [Hg] than other types of impacted systems. Se and As concentrations exceeded Canadian guidelines in 5% (aquatic life) and 0.2% of all fish, respectively. In mining areas, fish [Hg] were low and negatively correlated with [Se], and fish [Se] were positively correlated with [As]. In all areas, we observed an important overall and previously unpublished negative relationship between mean fish [As] and [Hg], suggesting an inverse consumption risk for these two elements. The ratio Se/Hg was lower than the protective value of 1 for 14% of all fish and was negatively correlated with fish length. However, the benefit-risk value (BRV) threshold, which accounts for the Se intake from other food products, did not suggest any fish consumption limitations, except for few very contaminated top predators (> 2 µg/g ww). More studies need to assess the role of Se against Hg toxicity and adjust fish consumption guidelines accordingly.

Keywords: Molar ratio, freshwater, benefit-risk value, guidelines, ecozones, anthropogenic disturbances

1. Introduction

Mercury (Hg) is a global contaminant that biomagnifies in aquatic food webs after its microbial methylation in anoxic conditions [1]. Natural phenomena and anthropogenic activities such as wildfire, reservoirs, and forest harvesting may favor the conditions leading to Hg methylation and trophic transfer [2]. Fish Hg bioaccumulation, mostly as methylmercury (MeHg) [3], is an issue at local and global scales through the harvesting of fish for daily human consumption [4, 5]. Risks related to Hg exposure has been especially high for developing children of mothers that were exposed through the consumption of

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aquatic top predators [6-8]. The threshold for sale of commercially harvested fish set by the Government of Canada is 0.5 μg Hg/g wet weight (ww) and the United States Environmental Protection Agency (US EPA) does not recommend eating fish with higher concentration [9, 10]. This threshold leads to an important number of advisories, limiting fish consumption even though this food resource also contains beneficial nutrients such as unsaturated fatty acids and selenium (Se) [11].

In the United States of America (USA), there were 30 million freshwater fish anglers (9% of the population) in 2016 [12], and Canadian anglers represented 7% of the total population. The most important fish species harvested in 2015 by Canadian anglers were walleye (*Sander vitreus*, 26%), Trout (*Salvelinus* sp., 20%), and Pike (*Esox lucius*, 13%) [13]. Excluding the Great Lakes anglers who were mostly fishing Walleye, the most popular fish harvested in the USA were Largemouth Bass (*Micropterus salmoides*), Trout, and panfish (small species that fit in a fry pan such as Yellow Perch, *Perca flavescens*) [12]. Indigenous communities of North America harvest fish for subsistence [14]; thus, their consumption is generally higher than the one of recreational North American anglers [15].

Several studies support the theory that Hg toxicity is related to a Se deficiency induced by the irreversible binding of Hg to selenocysteines, the active seleno-amino acid in selenoproteins [16-18]. For instance, Inuit with high blood Se/Hg ratio had the lowest prevalence of cardiovascular diseases [19], and a Chinese community exposed to Hg from mining waste that were given a high-Se yeast supplement (as selenomethionine) excreted more Hg than the people given the placebo [20]. Furthermore, their lipid peroxidation was reduced after 30 days of Se supplementation [20]. At high Hg concentrations, the Se-Hg

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binding could lead to a reduction of the selenoprotein activity [21, 22], which are important in many physiological functions such as the reduction of oxygen free radicals [23]. As most of Se in fish tissue is present as selenomethionine [24, 25], human Se intake from fish may increase Hg excretion and reduce the deleterious effects of Hg [20, 26]. However, after 50 years of studies about Hg-Se interactions, we still need to reach a consensus about the benefits of Se consumed from fish and other food products in the context of human Hg toxicity [16, 27].

A large number of studies suggest that a fish Se to Hg molar ratio (Se/Hg) lower than 1 would be low risk for fish consumers [17, 28]. However, few studies have explored the spatial, intraspecific and interspecific variation of this ratio [29]. It has been reported for fish in rivers, streams, and the sea, that the Se/Hg ratio is generally greater than one [11, 29], and sometimes reported to be a function of fish length [29, 30]. In freshwaters, data are limited, but important since geological Se occurrence and Se and Hg bioavailability vary greatly according to geographic region and waterbody type [31]. Other thresholds more representative of consumption risk than the Se/Hg molar ratio have been used in past research [32]. For instance, the benefit-risk value (BRV) takes into account the possible toxicity of Se, with a threshold set at a daily intake (PDI) of 72 nmol/kg body weight (bw)/day (400 µg/day for a 70 kg individual) [33, 34]. The BRV also considers that a minimum Se daily intake (10 nmol/kg bw/day) is necessary for normal physiological processes and that only the amount exceeding this requirement is available to counteract Hg toxicity.

Inorganic forms of As have a high potential toxicity [35]. In freshwater and marine fish, As is mostly on less toxic organic forms, but generally <1 to 20% of total As has been reported

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as inorganic As (iAs) in freshwater fish [36-38]. Interestingly, Zheng and Hintelmann [39] reported iAs proportions higher than 20% for three freshwater fish species from a highly As-contaminated lake [40], suggesting that the speciation of As in water may influence the fish tissue As speciation. Like Hg, iAs has a high affinity for Se in biological systems and thus, can compete with Hg for the biological Se-binding sites in cells. It is mostly the inorganic As forms (iAs) that are reported to bind to Se in cells [41]. Ouédraogo and Amyot [42] reported, for African freshwater fish, a modified Se/Hg molar ratio by subtracting fish [As] to the [Se] before the division by Hg ((Se-As)/Hg). Melgar et al. [43] modified the BRV to include the potential binding of As to Se (see Methods). Globally, few studies have considered the implications of this competition between Hg and As for Se-binding sites [42, 43]. Furthermore, Ouédraogo and Amyot [42] did not consider As speciation and Melgar et al. [43] did not calculate the daily Se intake from other food products than fish. Thus, it is timely to incorporate the potential cellular As binding to Se into risk assessment strategies, while considering a recommended maximum daily intake of As as 3.0 µg/g bw/day [44].

Exposure to contaminants such as As, Se, and Hg can greatly vary according to physiographic regions, ecozones, and anthropogenic disturbances such as mining activities [45, 46] and flooding by reservoirs [47]. Furthermore, biogeochemical processes are key to the transformation of these elements in freshwater systems, and thus to uptake by microorganisms and trophic transfer [31, 48-50]. These factors may greatly influence the fish bioaccumulation and human exposure through fish consumption. Thus, we collected data from 7815 fish, from 16 genera to (1) observe the spatial distribution of fish As, Hg, and Se concentrations and their relationships, across Canadian ecozones and with respect to anthropogenic activities; (2) calculate the Se/Hg molar ratios and investigate the main drivers

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of its variation in these fish; (3) evaluate how the average Canadian food consumption influences the molar intake of Se relative to Hg and As using the BRV; (4) explore the influence of [iAs] on the Se/Hg ratio in fish and on the BRV as a potential Hg competitor for the Se-binding sites in cells, and; (5) estimate fish lengths at which fish consumption advisory thresholds are reached.

2. Methods

2.1. Data collection

We gathered databases from government, private and academic sectors that simultaneously reported concentrations of total As, Hg, and Se concentrations in freshwater fish flesh. The database includes 7815 fish data from 1985 to 2018. We included some databases where [As] were not reported (2320 fish) but those of Hg and Se were. For Manitoba, fish data were obtained from the Water Quality Management Section 2017 of the Manitoba Sustainable Development (Winnipeg, MB, Canada). Quebec fish data came from the *Banque de données sur la qualité du milieu aquatique* from the *Ministère de l'Environnement et de la Lutte contre les Changements Climatiques* (MELCC, Quebec City, QC, Canada). Ontario fish data were from Chen and Belzile [51], Lescord et al. [52], and the Ministry of the Environment Conservation and Parks (MECP). Alberta fish data were from Alberta Health, and Donadt et al. [53]. Northwest Territories fish data were extracted from Stewart et al. [54]. All information about analytical procedures and quality controls are available in the Supplemental Information (SI) file (i.e., Section *Analytical procedures and quality controls*). All reference materials and quality controls for As, Hg, and Se were within the certified ranges for TORT-1, TORT-2 (lobster hepatopancreas, National Research Council of Canada

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(NRCC)), DORM-4 (Fish protein certified reference material for trace metals, NRCC), or SRM 1566b (Oyster tissue, National Institute of Standards and Technology).

2.2. Data preliminary treatment

For the Quebec database, fish flesh samples from 7 to 12 individuals of similar length were sometimes pooled for Se and As measurements, but Hg concentrations were measured on individual fish. As and Se concentrations from the pooled samples were assigned to individuals for which Hg concentrations were measured individually. All concentrations and ratios were log_{10} transformed to normalize data distributions. Given the large sample size, we visually evaluated if the data were normally distributed using Q-Q plot and density plots. Fish As, Hg, and Se concentrations (wet weight) lower than the detection limits were assigned values equal to half the detection limit, as per [55].

2.2. Data classification

Our dataset contained 7815 fish, representing 16 genera. According to the number of elements analyzed per sample, the number of samples varied (*n* range presented for each species where applicable). The genera, or the species (when only one species associated with a genus) were: *Ameiurus nebulosus* (Brown Bullhead; *n* = 37–81), *Ictalurus punctatus* (Channel Catfish; *n* = 24–30), *Moxostoma macrolepidotum* (Shorthead Redhorse; *n* = 24), *Catostomus* (Sucker, *n* = 654–827), *Stenodus leucichthys* (Inconnu; *n* = 49-61), *Prosopium williamsoni* (Mountain Whitefish; *n* = 10), *Coregonus* (Whitefish, *n* = 958–1254), *Lota lota* (Burbot, *n* = 83–136), *Hiodon* (Mooneye, *n* = 236–291), *Semotilus corporalis* (Fallfish, *n* = 10), *Esox lucius* (Northern Pike, *n* = 1002–1263), *Micropterus dolomieu* (Bass, *n* = 107–131), *Perca flavescens* (Yellow Perch, *n* = 291–554), *Sander* (Walleye and Sauger, *n* = 1655–

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2179), and *Salvelinus* (n = 432–1010). Given the relationship between [Hg] and fish length for top predators, we determined the fish length at a given threshold (see next section) for *Salvenilus namaycush*, *Esox Lucius*, and *Sander vitreus* given their high abundance (large sample size) and their frequent consumption by humans. Walleye, the most abundant species (i.e., 24% of all fish) was often used alone in modeling exercises to avoid bias from the species distribution among ecozone and anthropogenic activity groupings.

Ecozones were defined according to the National Ecological Framework Data (Fig. 1), physiographic regions according to the Geological Survey of Canada, and hydrography (river, lake, reservoirs) according to Hydro-Quebec, Manitoba Hydro (for the presence of reservoirs), and National Topographic Database ([56]). Anthropogenic activities affecting individual waterbodies were determined using several sources: mines were classified according to *Ministère de l'Énergie et des Ressources naturelles* [57], Manitoba Energy and Mines, and NTDB, smelters according to the United States Geological Survey. Agriculture activities were determined using NTDB, and forest harvesting activities, using *Ministère de l'Énergie et des Ressources naturelles* (QC) databases and NTDB.

The distance of a waterbody to either an agriculture and urban site within the watershed were classified as one of three levels: (1) 0–1 kms, (2) 1–5 kms, or (3) 5–10kms. Similarly, the distance of a waterbody to a mine in the watershed were classified as either 0–2, 2–4, 4–8, or 8–10 kms. Seven levels (i.e., 0–10, 10–30, 30–50, 50–80, 80–100, 100–130, 130–150 kms) were used to classify the distance of smelter to a waterbody. For each anthropogenic activity, these levels were tested by regressing the As, Hg, or Se concentrations as a function of the levels. Mine and smelter sites were considered in the same grouping. There were six lakes

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impacted by semi-precious mine sites (close to Chibougamau, QC). Five different types of smelters were included in this study; seven aluminum smelters in the province of Quebec, one copper smelter (Rouyn-Noranda, QC), one nickel smelter (Sudbury, ON), one lead and zinc smelter (Flin-Flon, MB), and one magnesium smelter (Haley Station, ON). When more than one anthropogenic activity occurred for a specific waterbody, it was indicated in our dataset but only the most important according to trace element influences, to our knowledge, was considered.

2.3. Threshold Calculations

Molar ratios of Se to Hg concentrations ([Se] / [Hg]) were calculated based on individual fish concentrations. To examine the influence of iAs (calculated as 20% of total As concentrations, a high-end estimate according to recent literature [38]) for its potential binding to cellular Se, we used the equation ([Se] - [iAs]) / [Hg]. We compared our ratios to two criteria, ratios of 1 and 4, according respectively to the abundant literature about the ratio of 1 and more recent research suggesting that 4 selenocysteines seem necessary to bind one MeHg molecule [17, 58, 59].

The benefit-risk value (BRV; nmol/kg body weight (bw)/day) developed by Zhang et al. [34] was calculated according to equations 1 and 2:

$$BRV_{Hg} = PDI_{Se} - MI_{Se} - PDI_{Hg} \quad (1)$$

$$PDI_{TE} = \sum(C_{TEi} \times IR_{i}) / bw \quad (2)$$

The recommended minimum intake of Se (MI_{Se}) is the amount required for normal physiological processes (10 nmol/kg bw/day) in a 70 kg individual (MI_{Se}; 55 µg/day) [44]. The probable daily intake of a given trace element (PDI_{TE}; nmol/kg bw/day) is the sum of the products of the element concentrations ($C_{TE,i}$; nmol/g) and the food intakes (IR_i; g/day) for each food item *i* (e.g., fish, flesh, poultry, eggs, beef, milk) divided by the body weight (70 kg). PDI_{Hg} was calculated on the assumption that Hg intake was only from fish products studied here. PDI_{Se} was calculated using individual fish data from this study and from the trace element concentrations in 2007 total diet study composites from Health Canada [60]. Ingestion rates were taken from the 2019 per capita disappearance of animal products (food available per person) from Agriculture and Agri-Food Canada [61], rice consumption (7.3 kg/capita/year) from Statistics Canada and milk IR from Speedy (Table S1, [62]). Fish consumption was calculated as the median from three studies (55.6 g fish/day); two of them were conducted in indigenous communities with relatively high daily consumption of fish [7, 62, 63]. Considering a meal as 250 g of fresh flesh, this IR would mean that about one meal would be consumed every 4 days. BRV results are interpreted as beneficial if they ranged from 0 to 72 nmol/kg bw/day [34]. BRV_{Hg} under 0 nmol/kg bw/day represented a molar Hg excess over Se and a BRV above 72 nmol/kg bw/day represents a Se intake that could be toxic (based on a maximum of 400 µg Se/day) [44].

As suggested by Melgar et al. [43], we adjusted the BRV_{Hg} to account for the interaction of iAs (calculated as 20% of total As concentrations, a high-end estimate according to recent literature [38]) as a potential Hg competitor for Se-binding sites in cells:

$$BRV_{Hg + iAs} = PDI_{Se} - MI_{Se} - PDI_{Hg} - PDI_{iAs} \quad (3)$$

where $BRV_{Hg + iAs}$ is the same as in equation 1 but further subtracting the PDI of iAs (PDI_{iAs}). PDI_{iAs} was calculated the same way as for the PDI_{Se} (Table S1).

2.4. Statistical analysis

We first conducted an exploratory factor analysis of mixed data (FAMD; R package *PCAmixdata*); this is equivalent to a principal component analysis (PCA) in that it combines the effects of continuous and categorical (i.e., mixed) variables. By this approach, we explored whether anthropogenic activities (categorical variable 1) or ecozones (categorical variable 2) explained any of the spatial variability in individual fish As, Hg, and Se concentrations (numerical variable 1, 2, and 3, respectively). We then tested if As, Hg and Se concentrations differed among anthropogenic activities by an analysis of variance (ANOVA) on raw data followed by a post-hoc Tukey parametric test. To compare the influence of As on Se/Hg ratios and on BRV_{Hg} (section 3.7), and to compare fish elemental concentrations between rivers and lakes, we used a Student's T test.

Simple regression analyses were performed between log_{10} transformed As, Hg, and Se molar concentrations (wet weight) and fish (*S. namaycush*, *E. lucius*, *S. vitreus*) length, for each anthropogenic activity. When relationships were significant and the visual assumptions of normality and homoscedasticity of the residuals were met (using Q-Q and density plots), we determined the fish length (x value ± SE) at specific thresholds ([Hg], [Se]/[Hg], ([Se]-[iAs])/[Hg], BRV_{Hg+iAs}) using the R package *chemCal* (CRAN, 2021; version 0.2.2). For [Hg], the threshold was 0.5 µg/g ww (2.5 nmol/g, log 2.5 = 0.4 nmol/g); for both ratios, the threshold was one (log 1 = 0), and the threshold for the BRV was 0. Confidence intervals (CIs) at 95% were calculated as the predicted length ± SE × 1.96 [64]. For each species mentioned above, fish length at a specific threshold was compared among anthropogenic activities and among thresholds within the same anthropogenic activity group using 95% confidence intervals. When these intervals did not overlap, we assumed a significant difference. The software R version 3.5.3, RStudio version 1.3.1056, and Sigmaplot 13 were used for all statistical analysis and graphing.

3. Results and Discussion

3.1. Global visualization of the data distribution

We obtained data from a total of 7815 fish from 175 sites in 142 waterbodies (Fig. 1). These included 112 lakes, 10 reservoirs, and 24 rivers. Reservoirs were often in a river continuum where other river sites were also sampled, thus the sum of lakes, reservoirs, and rivers (146) is higher than the number of waterbodies (142). The factor analysis of mixed data (FAMD) including ecozones (Fig. 2a) and anthropogenic activities (Fig. 2b) explained 27% of the variability in fish As, Hg, and Se concentrations. The small vectors for each element indicate the low percentages of variability explained by these two categorical variables. We performed two independent FAMDs; one with anthropogenic activities, and the other with ecozones to test which factor explained most of the trace elements variability. The FAMD for anthropogenic activities explained 38% of the variability in fish As, Hg, and Se concentrations and 31% was explained by ecozones. Thus, ecozones and anthropogenic activities were of similar importance in this model (i.e., only 7% difference in variance explained). Overall, in Fig. 2, the [Hg] vector was in the direction of reservoirs, agriculture, and urban sites, while the [Se] vector was directed towards sites impacted by mining activities. The [As] vector was directed towards unimpacted sites and was opposite to the Hg vector. From the comparison of both panels in Fig. 2, we observed that the majority of agriculture sites were in Prairies and Boreal Plains (i.e., in Alberta, Canada). Reservoirs and sites impacted by forest harvesting or mines were mostly in the Boreal shield (i.e., Quebec and Ontario). Unimpacted sites were present in all ecozones.

3.2. Anthropogenic and natural influences on fish Hg

Overall, we observed no difference in fish [Hg] between lakes and rivers ($p > 0.05$), but fish from reservoirs did present higher [Hg]. Taking only unimpacted sites, fish [Hg] were higher in lakes than in rivers (Fig. S1). Considering all fish genera, fish [Hg] increased in the following order of disturbances: mining < unimpacted < agriculture = urban < reservoirs < forest harvesting (note: only *Sander vitreus* was present in the group forest harvesting). Across anthropogenic activity categories, mean *Sander vitreus* [Hg], the most abundant fish species across ecozone and disturbance groupings, presented a similar pattern as for all genera (Fig. 3a), except that *S. vitreus* [Hg] were higher in unimpacted sites when compared to mining sites, and similar to agriculture sites and urban sites (Fig. S2a).

When considering all genera, 18% of fish had [Hg] higher than 0.5 µg/g ww;for Walleye, this proportion was 31%. Surprisingly, 65% of Walleye in Prairies had higher [Hg] than the guideline of 0.5 µg/g ww and this proportion was 64% in reservoirs. The highest [Hg] were found in reservoirs and sites impacted by forest harvesting. Flooded organic material found in reservoirs and organic matter flux from the watersheds impacted by forest harvesting can lead to conditions that are favorable for microbial Hg methylation in aquatic sediments [47, 65]. Increases in zooplankton and fish [Hg] have been observed following forest harvesting activities in lakes' watersheds [66, 67]. Mercury concentrations were among the highest (third rank) in sites impacted by urban activities. Indeed, wastewater may contain relatively high [MeHg] and the sediments in proximity to wastewater treatment plants may support microbial methylation, which acts as a MeHg source to the food web [68]. The lowest [Hg] were found in mining regions. As observed by Belzile et al. [69-71], high [Se] near mining

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operations can reduce microbial Hg methylation and lead to low Hg bioamplification in trophic webs (see also Section 3.6). One result of interest was the high Walleye [Hg] in the Prairies in contrast to the Boreal Plains of Alberta (Fig. S4a). Hall et al. [72] also observed that fish and cormorants from the Prairies ecozone bioaccumulate higher [Hg] than those in Boreal Plains lakes, potentially due to warmer temperatures and increased connections between lakes and wetlands; wetlands can be Hg hotspots for methylation, leading to higher MeHg exposure in adjacent aquatic food webs [72].

3.3.Anthropogenic and natural influences on fish Se

Overall, the lowest fish [Se] were found in reservoirs, compared to lakes and rivers. Fish [Se] were significantly higher in lakes than in rivers, but this trend was influenced by the high number of mining region lakes. Indeed, in unimpacted sites, the [Se] were similar between lakes and rivers. In sites impacted by agriculture and urban activities, fish [Se] were higher in rivers than in lakes (Fig S1). The highest fish [Se] were measured in mining regions, and in sites influenced by forest harvesting activities. Sites impacted by urban and agricultural activities had intermediate [Se]. Fish [Se] were significantly lower in reservoirs and unimpacted sites. For Se, the results were similar for the all-genera analysis (Fig. 3b) and the Walleye-only analysis (Fig. S2b) because [Se] were not related to fish length for most genera ($p > 0.05$) and was generally similar among species from the same waterbody [46, 73]. Walleye had notably lower [Se] in the Boreal Plains, Hudson Plains, and the Taiga Plains than in other ecozones (Fig. S4b).

There is no threshold for fish [Se] in the Canadian guidelines for human consumption. Only 5% of our fish exceeded the new Canadian Se guidelines for protection of the environment based on whole fish [Se] (6.7 µg/g dw, 1.3 µg/g ww). Mining and agriculture impacted sites are known to have high [Se] [31]. Indeed, sulfide minerals from semi-precious metal mining areas and agricultural soils from semi-arid regions that are formed of sedimentary shales may contain high [Se] [31]. We did not find many studies that reported high [Se] in sites impacted by urbanization, excepted the case of the San Francisco Bay where the Se sources were mostly coming from irrigated agricultural soils and to a lesser extent, from oil refineries [74]. Landfill leachates may also be a source of Se [75]. Fish from sites impacted by forest harvesting activities also had high [Se] (Fig. 3b), but we did not find any study that has reported this trend previously. Fish from reservoirs had among the lowest [Se] and the highest [Hg] (Fig. 3a and 3b), which resulted in the lowest Se/Hg ratios (Fig. 3d), invoking a potential risk for fish and their consumers (see below Section 3.5).

3.4. Anthropogenic and natural influences on fish As

Comparing waterbody types, fish [As] were highest in rivers, lower in lakes and the lowest concentrations were found in reservoirs. Considering all genera, the highest [As] were measured in fish from mining regions and unimpacted sites (Fig. 3c). Many sites classified as unimpacted were in the Hudson Plains, the Taiga Plains, and the Mixed Wood Plains which were all presenting relatively high [As] (Fig. S3c). Fish [As] were also high in sites with agriculture in the watershed (3rd rank). The lowest fish [As] was measured in reservoirs, and sites impacted by forest harvesting and urbanization, interestingly contrasting with [Hg] (see Section 3.6). Fish muscle [As] were generally lower than the Canadian threshold for fish consumption (3.5 µg/g ww; Fig. 3c). Of the 7815 fish analyzed, only 12 individuals from the genus *Coregonus* and one Northern Pike had [As] higher than 3.5 µg/g ww. Those fish were collected in the Mackenzie River (NT, 10 *Coregonus*) and the Hudson Plains (Attawapiskat

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and Moose Rivers, ON). All these river systems have coastal confluences, and it is possible that marine inputs are influencing [As] in these fish. Based on their total [As], these fish were also the only ones that led to a daily As intake greater than 3 µg/g bw/day, the threshold set by the World Health Organization [44].

Arsenic concentrations in our freshwater fish (geometric mean of 0.65 µg/g ww) were generally much lower than those reported for marine fish (4–60 µg/g ww) in the review from Bosch et al. [76]. Arsenic enrichment is a well-known phenomenon in semi-precious metal mining and smelting regions such as Sudbury (ON), Rouyn-Noranda (QC), and Flin-Flon (MB) [77-79]. Lescord et al. [52] measured As, Hg, and Se concentrations in fish flesh from rivers and lakes located in the Hudson Plains ecozone and observed that riverine fish collected close to the river mouth (in proximity to Hudson Bay) had higher [As] than specimens of the same species sampled further upstream, or in lakes. Fish with higher [As] in lower river reaches, close to Hudson Bay, maybe anadromous or predators of anadromous fish and therefore more exposed to marine As sources [80]. It is therefore important to understand the factors influencing As concentrations and speciation in freshwater fish. Indeed, in contrast to marine fish with high total [As] and a high proportion of arsenobetaine (AsB), [As] are lower in freshwater fish and the chemical speciation is more variable, thus making the risk assessment for consumers more challenging [38].

3.5. Anthropogenic and natural influences on fish Se/Hg ratio

Overall, we did not observe a significant difference between the average Se/Hg ratio in lakes and rivers ($p > 0.05$), but we saw differences comparing lakes and rivers by anthropogenic activity grouping (Fig. S1). For example, fish [Hg] from unimpacted sites (i.e., the grouping

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with the highest degrees of freedom, >1294) are higher in lakes than in rivers according to a T test ($p < 0.001$), but fish [Se] were similar ($p = 0.66$). Therefore, the Se/Hg ratio is lower in lakes than in rivers. In contrast, for agriculture sites, the fish [Hg] were similar between lakes and rivers (T test, $p > 0.05$), but the fish [Se] were significantly lower in lakes than in rivers ($p < 0.001$, df > 399). Thus, the Se/Hg ratio is higher in rivers from agriculture sites, when compared to lakes. The differences between lakes and rivers are driven by Hg in unimpacted sites, but by Se in agricultural sites.

Given the low Hg and high Se concentrations of fish near mining sites, the highest Se/Hg ratios were measured in mining regions. Sites impacted by agriculture had the second-highest ratio for all fish as well as within Walleye. Pooling all fish, intermediate Se/Hg ratios were measured in unimpacted and urban sites, and the lowest ratios were measured in sites impacted by reservoirs and forest harvesting (Fig. 3d). For Walleye, the trend was similar, but differences (from the ANOVA) were not as clear as for all fish (Fig. S2d). Overall, the Se/Hg ratios were rarely under 1 in fish studied herein (Fig. 1). In total, 14% of fish had a ratio lower than 1 and this proportion rose at 19% when considering only Walleye, irrespective of anthropogenic impact classification or ecozone. For this species in reservoirs, 52% of individuals had a Se/Hg ratio lower than 1.

Se/Hg ratios lower than 1 have rarely been reported in the literature for freshwater fish. As an example, Peterson et al. [29] reported only 2.5% of 468 stream fish from the Western United States had a ratio lower than 1. Given that Hg methylation is often higher in lakes than in rivers or streams [81], our higher proportion of fish with low Se/Hg ratio could be explained by the high number of lakes in our study, compared to Peterson et al. [29], and our

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observed differences between lakes and rivers (Fig. S1). Given the low ratios measured in reservoirs (because of the significantly higher fish [Hg], and lower [Se] than other anthropogenic activity groupings), more studies are necessary to investigate fish health as a function of the Se/Hg ratios, and assess if artificially adding Se in reservoirs could be beneficial for these Hg-impacted ecosystems [82].

The human diet derives considerable Se amount from other food sources than fish, especially livestock (Table S1) [83]. When these sources are considered, the Hg benefit-risk value (BRV_{Hg}) was always greater than 22 nmol/kg bw/day and well above the threshold of 0 nmol/kg bw/d (Fig. 3e). It should be noted that we did not account for Hg intake apart from fish consumption, and marine fish intake was also excluded for the purposes of this study about freshwater fish. Furthermore, some Indigenous communities with higher consumption of wild food sources could have a lower Se intake than the one calculated herein given that domestic livestock diets are supplemented with Se [83]. We noted extreme BRV values close to both thresholds (Fig. 3e). For mining sites, some fish individuals yielded BRVs that reached the threshold of human Se toxicity risk (72 nmol/g bw/day). These were Rouyn and Hannah lakes, two lakes known for their historical trace element contamination, including Se [46, 48, 84-86]. These specimens had an average [Se] of 5.9 ± 0.8 µg/g ww (n = 37), higher than the new threshold for the protection of the environment (1.3 µg/g ww), which is also used by the US EPA [87]. At the other end, large specimens from reservoirs led to BRV < 0 (Fig. 3e). Note that fish from reservoirs presented the lowest [Se]. Thus, even if the human Se intake is high from other food sources than fish, some top predator meals with [Hg] higher than 2 µg/g ww, eaten once every 4 days, could cause a risk according to our calculations, as reported in other toxicological studies [88].

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The study of Zhang et al. [34] reported a BRV_{Hg} of 9 ± 21 (± SD) nmol/kg bw/d in China, which is lower than our estimate for Canadians (26 ± 6 (± SD) nmol/kg bw/d). Given that the Chinese population eats more rice (600 g/day) and less meat (84 g/day), their Se intake is likely lower than the one of North Americans. In fact, more than 50% of the Chinese Hg and Se intake comes from eating rice [34]. Only one other study to our knowledge has calculated the BRV but did not estimate the daily Se intake [43]. More risk assessments need this tool given the important variation in the Se intake around the world [89].

A recent study suggested that 4 selenocysteines present in the selenoprotein P are necessary to bind one MeHg molecule in animal liver to allow demethylation of MeHg into mercury selenide (HgSe) particles [17]. Given this stoichiometry, fish having a Se/Hg ratio higher than 4 would be better for human consumption. Only 42% of all fish analyzed in the current study had Se/Hg > 4 in muscle tissue (Fig. 3d). According to Ponton et al. [46] and Khadra et al. [90] working with yellow perch, [Se] is about two times higher in liver than muscle, and according to the same study [90], [MeHg] is 5 times lower in liver than in the flesh, suggesting that fish livers may have a higher Se/Hg ratio more suitable for detoxification compared to muscle tissue. Manceau et al. [17] observed that HgSe was only present in fish and bird liver, and not muscle, suggesting that the Se/Hg of 1 is mostly applicable for liver when considering the organism health. When considering flesh, the ratio Se/Hg is not informative of this tissue health since the Hg in muscle is not principally bound to Se, but to sulfur. The ratio Se/Hg in fish flesh is rather informative on the relative consumer intake of both elements.

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3.6. Correlations between As, Se, and Hg in fish?

We observed an important and significant negative relationship between mean [As] and mean [Hg] calculated based on anthropogenic activities (Fig. 4; means taken from Fig. 3a and 3c). This negative trend was present when data from all fish were pooled and when only considering Walleye (Fig. 4). These negative relationships were also strongly significant when concentrations from individual fish were plotted ($p < 0.001$ for all genera and Walleye) but means provide a better visualization of the anthropogenic influences. This relationship suggests that Hg methylation, at the base of the food webs, and subsequent MeHg bioaccumulation in the trophic chains leading to fish is higher in sites where As bioaccumulation is lower. We hypothesize that in sites with higher Hg methylation potential, higher microbial synthesis of As organic forms [91]. These organic As species have a lower relative biological uptake rate compared to inorganic As species, as suggested by axenic algal, and insect larvae uptake rate studies, of several As species [92, 93]. Thus, the formation of organic forms of Hg and As, at the base of the food webs, may lead to contrasting bioaccumulation patterns, as observed in Fig. 4. A simultaneous microbial synthesis of organic Hg together with organic As by the same or different taxa is highly probable in an aquatic system [91, 94]. Strong evidence suggests that Hg and As microbial processing genes (*hgcA* and *arsC*) are close to each other in a vast diversity of bacterial genomes, suggesting that parallel microbial transformation of both elements may be possible [95]. This hypothesis needs further investigation, including the link between the As speciation in water and sediments, and the accumulation in aquatic organisms [96]. Broadly speaking, the negative relationship between Hg and As (Fig. 4) suggests that As exposure to humans from fish consumption is less when Hg exposure is higher, and vice versa.

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No evidence of a relationship between Hg and Se concentrations was found in our fish, except in mining regions where [Hg] was negatively correlated with [Se] in the Percidae family (*Sander* and Yellow Perch) (Fig. 5a). This negative relationship has been previously reported in the Sudbury (ON) area (a region included in the current dataset) and elsewhere [71, 97, 98]. A recent study on the influence of Se on Hg bioaccumulation in fish of the Sudbury mining region (i.e., nickel mining) reported that even after a decade of reductions in smelter Se emissions, the reduced MeHg bioaccumulation is still correlated with Se exposure [69]. Selenium has been shown to reduce Hg methylation in sediments by the microbial formation of stable HgSe [70].

Due to the absence of a positive correlation between both elements and the known high proportion of Hg as MeHg in fish muscle, our results do not suggest the formation of agglomerates of HgSe in fish muscle, in contrast to what has been observed in fish and mammal livers [99, 100]. Indeed, recent speciation analysis of fish tissue revealed that MeHg in muscle was not bound to selenocysteine in selenoproteins but to cysteine (MeHg-cysteinate), in contrast to the liver where MeHg was bound to selenocysteine of selenoprotein P or in the form of HgSe particles [17]. However, the fact that Hg and Se are not bound in fish muscle does not necessarily suggest that the Se/Hg ratio should not be used in risk assessment strategies, since it represents the proportional amount of both elements consumed by predators, including humans.

We observed a positive relationship between Se and As concentrations, only for fish from semi-precious metal mining regions (Fig. 5b). This relationship (with the Percidae family) may be due to a co-exposure of both contaminants, but also to a cellular complexation of

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both elements in fish tissue [59]. High As exposure in mining regions could have led to a higher proportion of inorganic As in tissues, compared to less impacted environments [39]. Indeed, the relationship in Fig. 5b appears stronger at higher Se and As concentrations. The low Hg accumulation in fish from mining regions could have positively influenced the binding of As to cellular Se-binding sites. Indeed, As, cadmium, and Hg in rat liver have been shown to influence the mitochondrial Se metabolism by the binding of these metals to Se in cells [59, 101].

3.7. Influence of As on fish consumption risks

Arsenic species in fish flesh are numerous, but AsB is the dominant form both for marine and freshwater fish [38, 102]. The study from Tanamal et al. [38] with freshwater fish from Yellowknife (NT, Canada) reported that 0 to 20% of total As was in the potentially toxic inorganic forms, while dimethylarsenic (DMA) was also in high proportions in some lake/species combinations. It has been shown that AsB is stable during cooking [103, 104] and digestion [105], has very low toxicity [102], and is excreted rapidly [102]. As a result of the iAs methylation by the human body, DMA is the main product, and also known to be less toxic than monomethylarsenic (MMA), arsenite (As(III)) or arsenate (As(V)) [106]. Given that most of the As in fish is in organic chemical forms that are not known to be toxic [38], we considered that a maximum of 20% of total As, the inorganic portion (iAs), would be a potential competitor of Hg to the Se-binding sites in cells.

Adjusting the Se/Hg ratios for this 20% fraction of total As ((Se-iAs)/Hg) reduced them significantly, but not for all anthropogenic activity groupings (Fig. 6a). Because higher [Hg] corresponds to lower [As] (Fig. 4), adjusting for iAs does not significantly reduce the Se/Hg ratio for two of the six anthropogenic activity groups with high [Hg] and low [As] (urban sites and reservoirs) (Fig. 6a). Overall, even if adjustment for iAs significantly changed the Se/Hg ratios, the mean ratios remain higher than 1 across all anthropogenic activities (Fig. 6a).

The BRV_{Hg} was also tested following adjustment for iAs (20% of total As) as a potential competitor for Se-binding sites ($BRV_{Hg + iAs}$; Fig. 6b). The iAs adjustment significantly reduced BRV_{Hg} for all anthropogenic activity groupings but the $BRV_{Hg + iAs}$ values remained well above the threshold of 0 nmol/kg bw/day with mean values > 22 nmol/kg bw/day (Fig. 6b). When the $BRV_{Hg + iAs}$ was recalculated considering the consumption of only marine fish with a [total As] of 7.4 µg/g ww and 20% of this concentration as iAs [60], which is much higher than the [As] from our freshwater fish (0.65 µg/g ww), the $BRV_{Hg + iAs}$ was on average 25 ± 7 (± SD) nmol/kg bw/day. As mentioned earlier, large top predators with [Hg] > 2 µg/g ww may lead to BRV values close to 0 if eaten every four days. Overall, our results suggest that even when considering the iAs as a potential competitor of Hg for Se-binding sites, calculated daily intake of Se seems higher than the sum of both iAs and Hg daily intake [34, 44].

3.8. Fish length at thresholds

It is well known that [Hg] in predatory fish increases with fish length [107]. To be allowed for commercialization, fish should have [Hg] lower than 0.5 µg/g ww according to Health Canada and US EPA [9, 10]. For genera that are mostly non-piscivorous including *Perca*, *Lota*, *Coregonus*, *Ameiurus*, *Catostomus*, and *Hiodon*, their [Hg] were generally lower than 0.5 µg/g ww, and their Se/Hg ratio generally lower than 1, no matter the perturbations and ecozones (Fig. S5). In contrast, predatory fish from the genera *Esox, Micropterus, Sander*, and *Salvelinus* had [Hg] often higher than 0.5 µg/g ww. Considering the trend between [Hg] and fish length, we calculated the fish length above which consumption is not recommended for each of the three anthropogenic activity groupings that provided the greatest contrast in fish [Hg] and [Se] (Fig. 7). For Walleye, predicted [Hg] reached 0.5 µg/g ww at predicted lengths of 754, 359 and 444 mm in mining regions, reservoirs, and unimpacted sites, respectively (Fig. 7). The Se/Hg ratio is also a function of fish length, but it is driven mostly by fish [Hg] because [Se] varies much less with respect to fish length. Very few Walleye had Se/Hg ratios < 1 in mining regions. The Se/Hg ratio declined with fish length and reached 1 at predicted lengths of 422 and 489 mm in reservoirs and unimpacted sites, respectively (Fig. 7). Both BRV_{Hg} (Fig. 7) and $BRV_{Hg + iAs}$ (not presented) were also functions of fish length for Walleye ($p < 0.05$) but exceeded the threshold value of 0 nmol/kg bw/day at all body sizes.

Predicted fish lengths at given thresholds are summarized in Fig. 8 for the species *Sander vitreus*, *Salvelinus namaycush* and *Esox Lucius*, for the 6 identified perturbations. Predicted Walleye length at [Hg] = 0.5 µg/g ww and at Se/Hg = 1 were significantly lower in unimpacted sites and reservoirs compared to mining regions (Fig. 8). Generally, the fish lengths at thresholds were similar for [Hg], the Se/Hg ratio, and the (Se-iAs)/Hg ratio. Our comparisons suggest that the Hg threshold seems generally conservative even considering the Hg interaction with Se. Fish length at the Hg threshold was also very similar to the fish length at another threshold i.e., the Health Canada provisional tolerable daily intake of 0.47 µg/kg bw/d. These results contrast with those of the BRV values. The fish length at this threshold (BRV = 0) was never reached because of its high value (Fig. 3e). No matter the

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size of fish, there was never enough Hg, or both Hg and iAs, to statistically use all Se-binding sites given the high Se concentrations from the average Canadian diet, and to a lower extent, from fish intake.

4. Conclusions and Perspectives

Our study suggests that anthropogenic activities influenced the fish exposure and accumulation of As, Hg, and Se to different extents. We also observed an influence of ecozones, and evidence of elemental interactions that potentially occurred within the fish and their respective environments. The [Hg] threshold for fish commercialization (0.5 µg/g ww) led to similar advisory recommendations as the Se/Hg ratio which was generally lower than 1 mostly for large fish with elevated Hg concentrations (i.e., > 0.5 µg/g ww). Given the negative relationship observed between Hg and As in fish, more studies are needed to understand As bioaccumulation, biotransformation, and trophic transfer of several As chemical species in freshwater organisms. The beneficial impact of Se to reduce Hg toxicity to humans also needs further investigations since estimated Se daily intake from food products other than fish is high. Consequently, there seems to be enough Se to bind Hg in human cells considering the Benefit-Risk Value (BRV), with some exceptions for top predators with very high Hg concentrations (> 2 µg/g ww) eaten every 4 days, and for people with low Se intake.

Declaration of interests

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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Figure Captions

Figure 1. Map of Canada showing ecozones and sampling sites. Sites are color-coded to show mean muscle Se/Hg ratios (see legend) in all fish sampled.

Figure 2. Factor analysis of mixed data (FAMD) including As, Hg, and Se concentrations in fish muscle (all sampled fish included) as numerical variables and ecozones (a) and anthropogenic activities (b) as categorical variables. For (a) and (b), the same FAMD is presented, but coloring different categorical variables.

Figure 3. Fish muscle mercury (a), selenium (b), and arsenic (c) $\log_{10}$-transformed concentrations (nmol/g wet weight), the ratio of the molar selenium to mercury concentrations (Se/Hg) (d) and the benefit-risk value (BRV, nmol/kg body weight/day) (e). Means are represented by blue dots and boxplot width varies according to the number of samples and notch are 95% confidence intervals. Means that do not share the same letter were significantly different. The dashed red line in the panel (a) is 0.5 µg/g ww, the solid red line in the panel (c) is 3.5 µg/g ww, the orange and red dashed lines in the panel (d) correspond to ratios of 4 and 1, respectively, and the dashed red lines in the panel (e) are BRVs of 0 and 72.

Figure 4. Mean muscle mercury concentrations ($\log_{10}[Hg]_{fish}$, nmol/g wet weight (ww)) as a function of mean arsenic concentrations ($\log_{10}[As]_{fish}$, nmol/g wet weight (ww)) for all fish genera (circles) or Walleye (*Sander vitreus*) only (triangles). Means calculated for each

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anthropogenic activity grouping. For sites impacted by forest harvesting, only *Sander* were sampled.

Figure 5. Log_{10}-transformed muscle mercury (a) and arsenic (b) concentrations (nmol/g wet weight) as a function of muscle selenium concentrations (nmol/g wet weight) in fish from the family Percidae sampled from mining regions. Symbols are individual fish, dashed reference lines represent one-to-one agreement in concentration, and solid lines represent fitted OLS regressions.

Figure 6. Boxplots comparing (a) the fish muscle ratios Se/Hg and (Se-iAs)/Hg and (b) the fish muscle BRV_{Hg} and BRV_{Hg+iAs} for each of six anthropogenic activity groupings. Stars indicate significant difference between the two ratios and the two BRVs within each anthropogenic activity according to a student T test (with *p* value).

Figure 7. Log-transformed Walleye (*Sander vitreus)* mercury, and selenium concentrations (Log nmol/g wet weight (ww)), selenium to mercury concentrations ratio (Se/Hg), and the benefit-risk value (BRV_{Hg}, nmol/kg body weight/day) as a function of Walleye total length from mining regions (left), reservoirs (centre), and from unimpacted sites (right). Horizontal reference lines correspond to the Canadian threshold for fish commercial sale in [Hg] plots ([Hg] = 0.5 µg/g ww), the 1:1 molar ratio in Se/Hg plots, and the BRVs = 0 and 72 in BRV plots. Solid vertical lines indicate predicted mean fish lengths at threshold values and vertical dashed lines are 95% confidence intervals.

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Figure 8. Predicted total fish lengths (means ± 95% confidence intervals) at which specified toxicological thresholds are reached in each of six anthropogenic activity categories for (a) *Sander vitreus*, (b) *Salvelinus namaycush*, and (c) *Esox lucius*. Thresholds are 2.5 nmol/g (0.5 µg/g ww) for mercury (Hg), 1 for both Se/Hg and (Se-iAs)/Hg) ratios, and 0 for benefit-risk values (BRV_{Hg+iAs}). Fish lengths extending to the right edge of the plot indicate that even the largest fish caught would not reach the threshold value. The maximum fish length (right end of *x* axis) is taken from our dataset. Absent bars are insignificant relationships between the threshold category and fish length. Letters indicate significant differences between fish length at threshold from the same panel. No letter indicates no significant differences.

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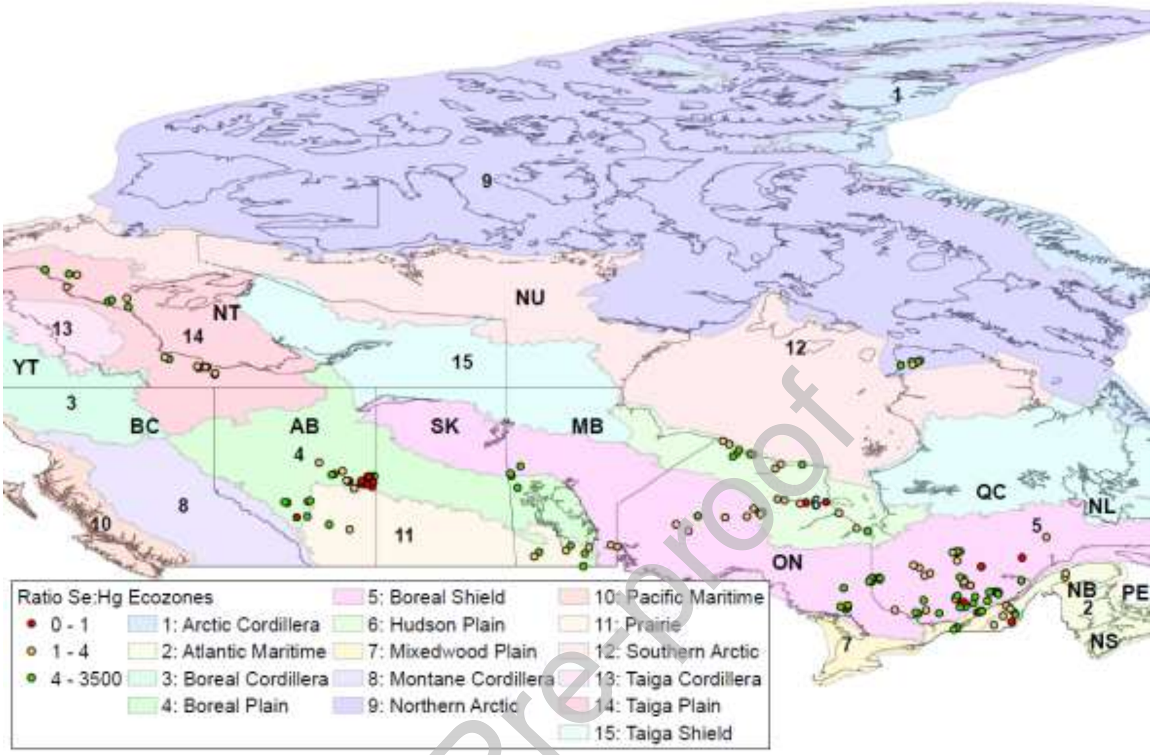

Figure 1; see map attached

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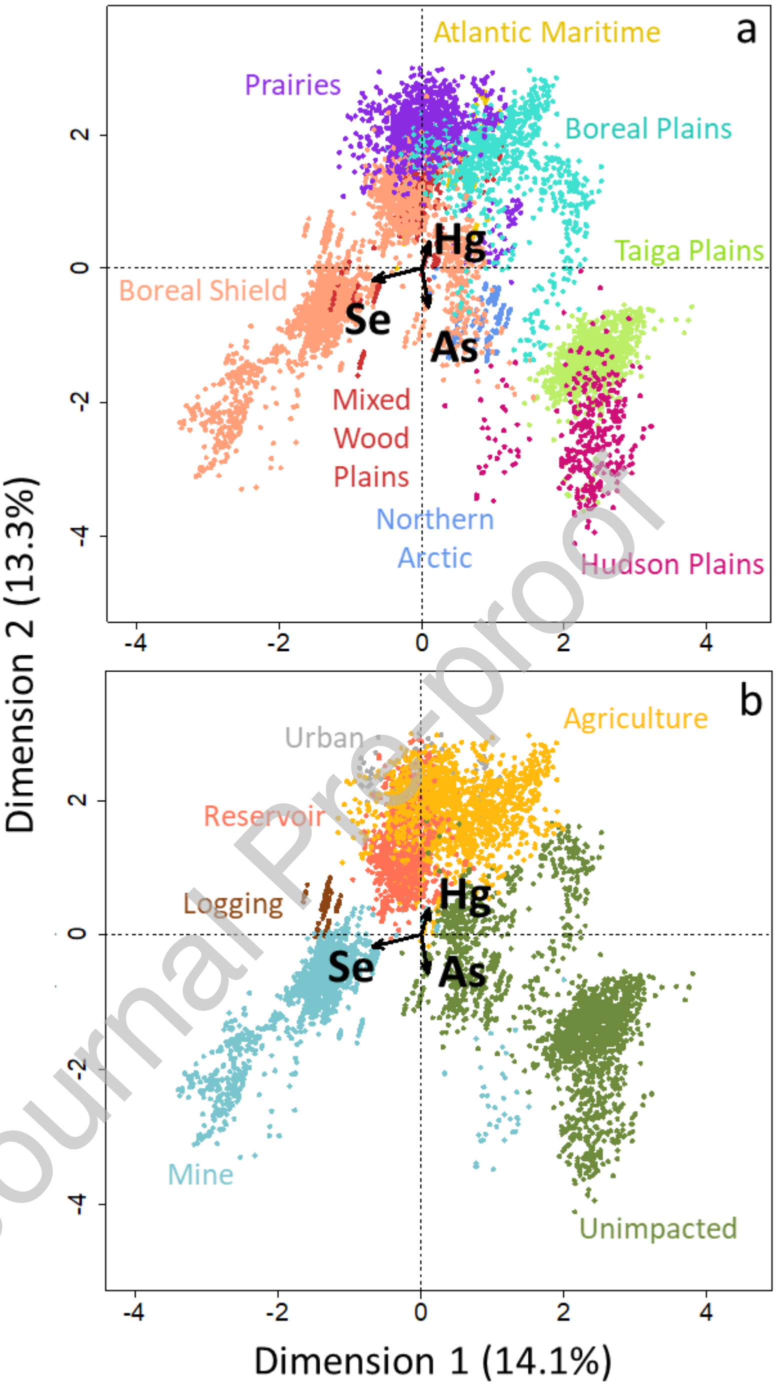

Figure 2; Ponton et al. 2022

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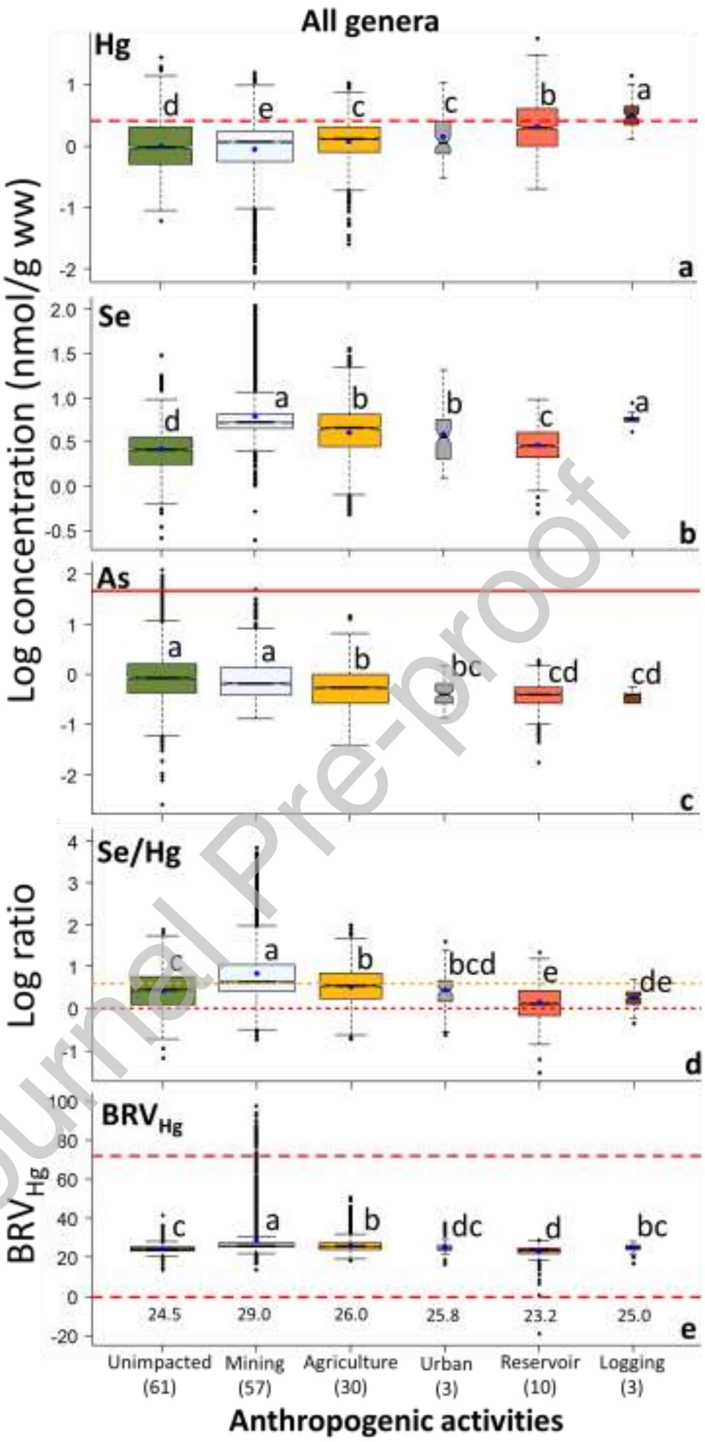

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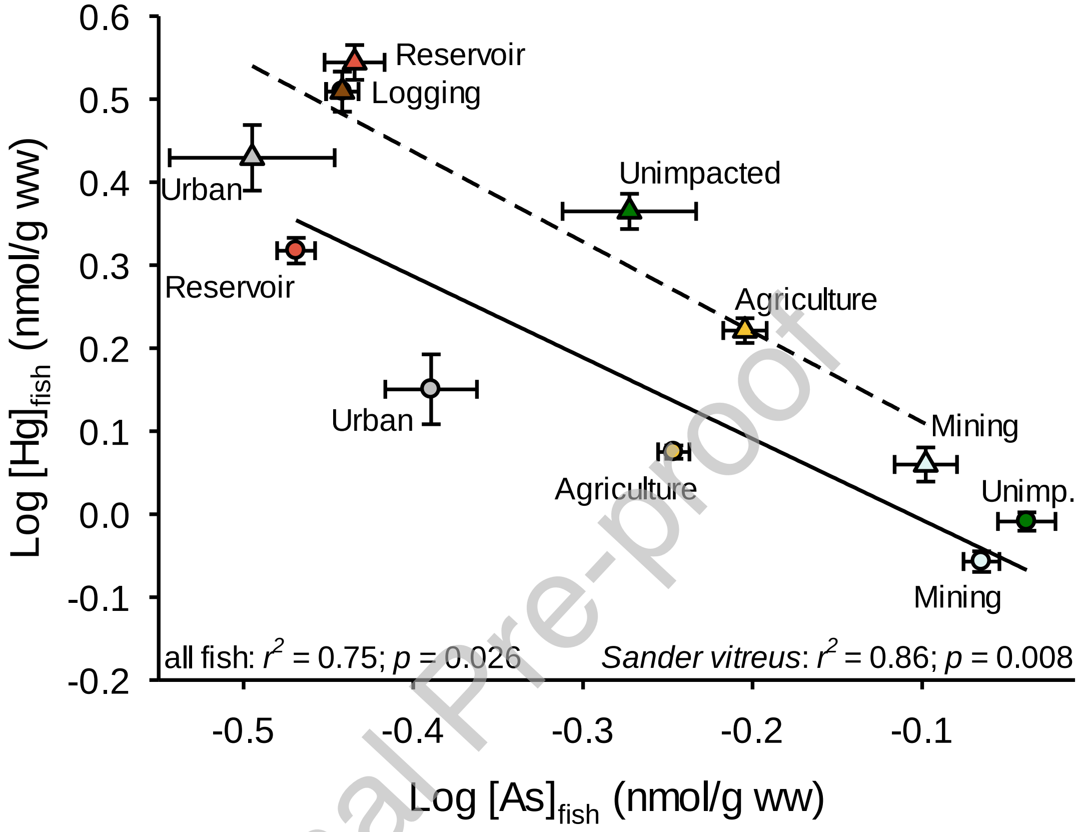

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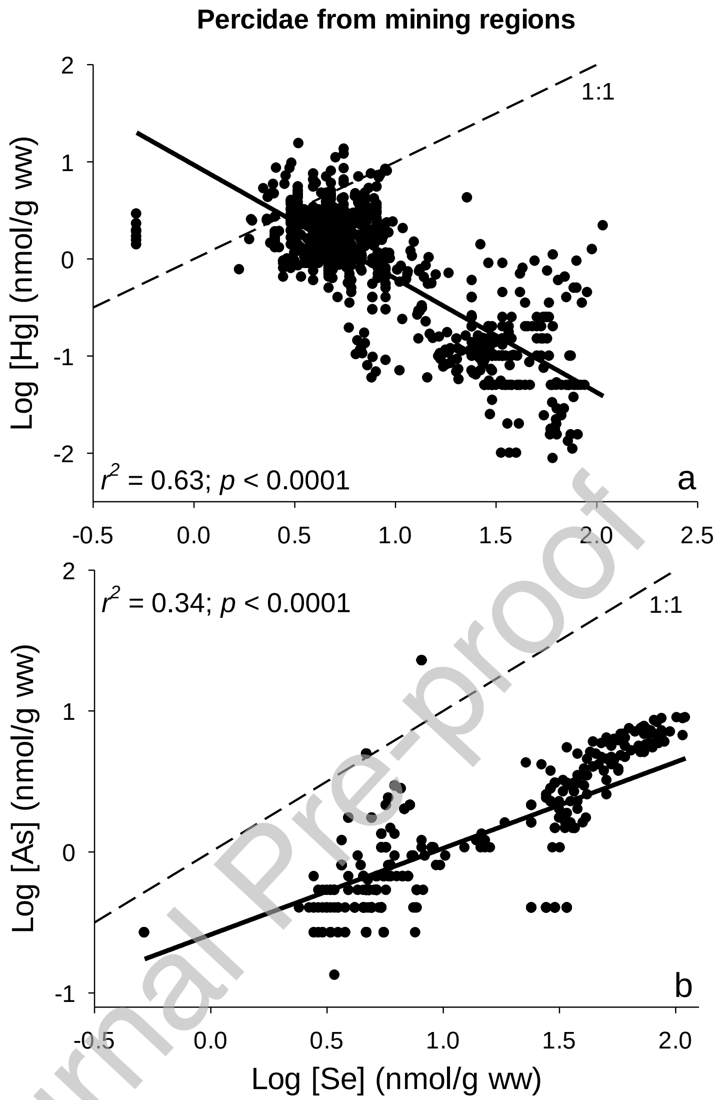

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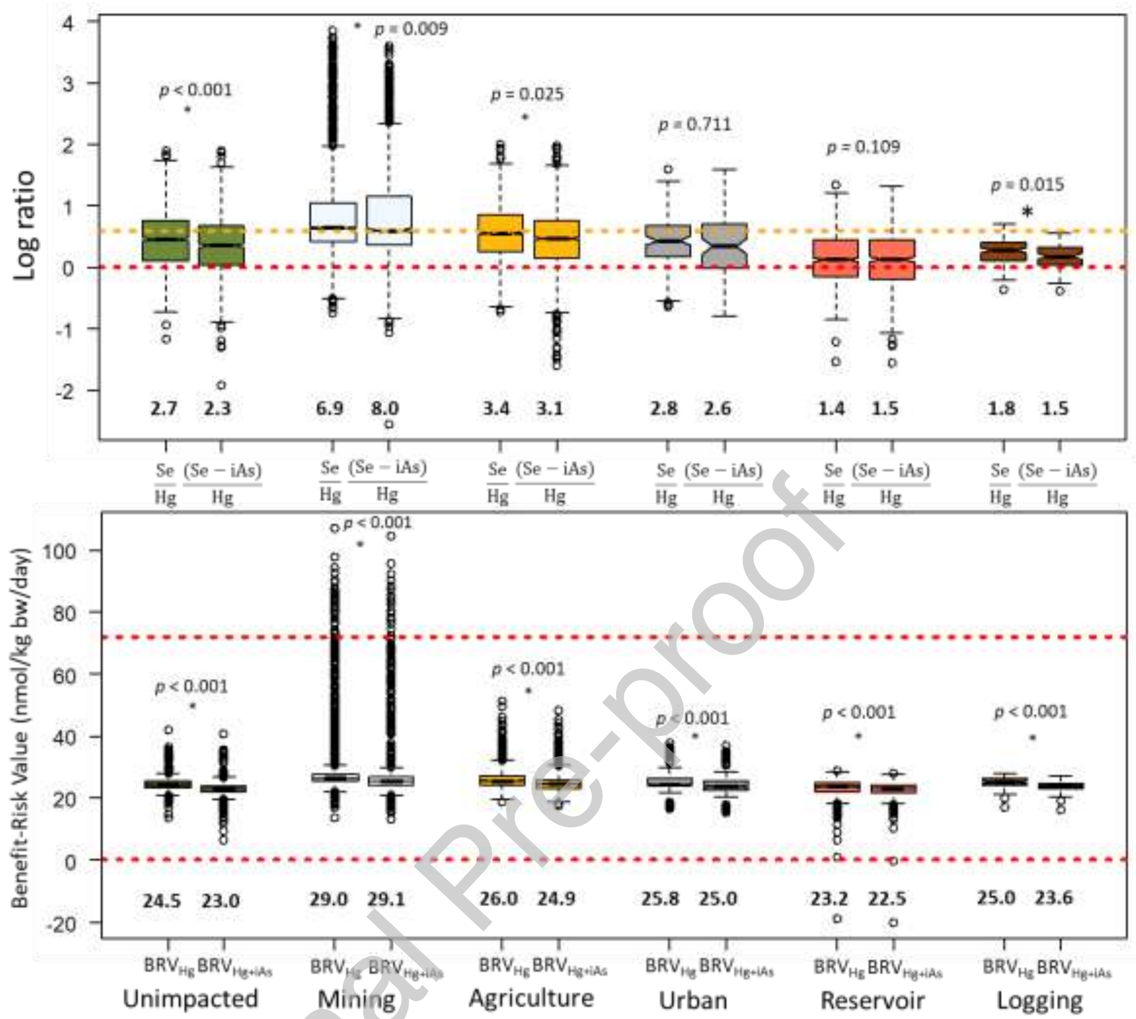

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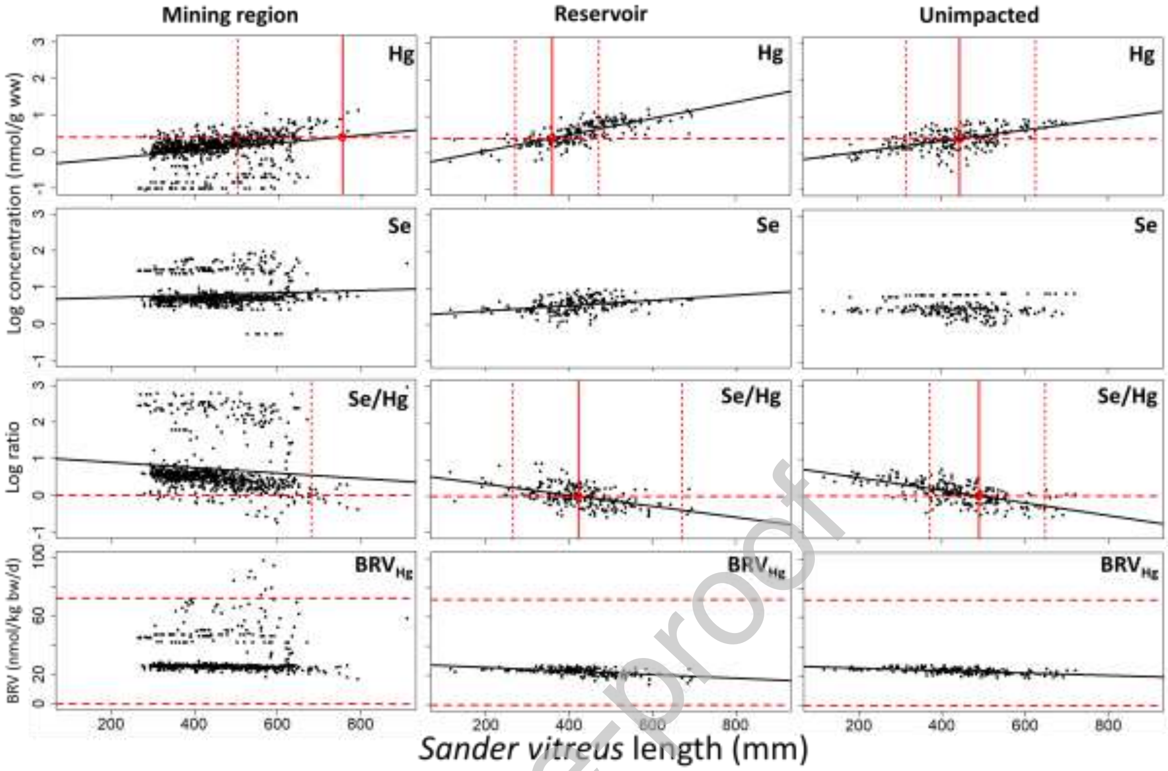

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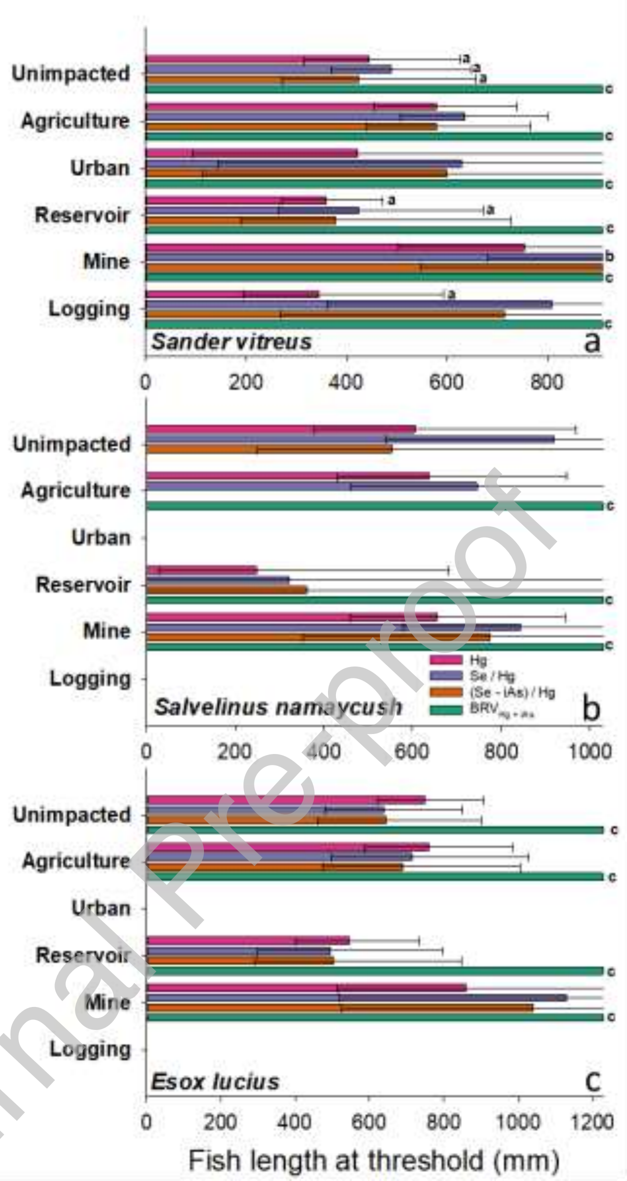

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