

A Review of Human Health Impacts of Selenium in Aquatic Systems



**A report submitted to the
International Joint Commission by the
Health Professionals Advisory Board**

July 24, 2020

Acknowledgements

The Health Professionals Advisory Board (HPAB) of the International Joint Commission (IJC) would like to acknowledge the excellent efforts of the Great Lakes work group and other contributors and reviewers of this health review, as identified below.

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On the front cover: Woman fly fishing, Wisconsin Department of Natural Resources, USA

Executive Summary

The Health Professionals Advisory Board (HPAB) has undertaken a human health review of selenium at the request of the International Joint Commission (IJC) and developed this technical report with the assistance of contractor Michael Kosnett. Selenium is an essential nutritional element that supports the health of immune, metabolic and reproductive systems. Exposure and uptake occur predominantly through the diet. However, when humans regularly consume above recommended upper intake levels for adults (400 micrograms/day), health problems can occur.

Selenosis is the condition resulting from chronic selenium intoxication; symptoms include diarrhea, nausea, fatigue, muscle aches and hair and nail damage or loss. Selenium occupies a unique position in environmental public health because of the narrow margin between intake that is nutritionally sufficient and that which is hazardous. Selenosis has been linked to human consumption of animals and foods from waters and soils contaminated with unnaturally high levels of selenium.

Widely available and used nutritional supplements are another contributor to selenosis and must be considered in setting safe environmental levels. Toxic human environmental exposure to selenium may occur when selenium levels accumulate in the ecosystem via leaching from mining waste into aquatic systems, anthropogenic emissions from the burning of coal or other industrial activities which accumulate in fish and wildlife. Widespread negative impacts on sensitive ecosystems and human health due to elevated selenium concentrations are anticipated for areas with high geologic selenium concentrations and expanding industrial and mining operations. The IJC advised governments on a similar issue in response to a reference from Canadian and US governments pursuant to Article IX of the Boundary Waters Treaty of 1909. Its final report, “Impacts of a Proposed Coal Mine in the Flathead River Basin,” examined and reported on relevant water quality and quantity issues in the basin, (IJC 1988).

Some environmental health research connects regular consumption of high levels of selenium—above recommended maximum levels—to health issues such as prostate cancer and neurotoxicity. Ongoing research also is exploring the relationship, either harmful or beneficial, between low-level selenium intake and chronic health conditions such as heart disease, diabetes and cancer (Kenfield et al. 2014; Kristal et al. 2014; Mao et al. 2014; Rayman and Stranges, 2013; Rees et al. 2013). A screening assessment by Environment and Climate Change Canada (ECCC) and Health Canada considered risk to human and environmental health posed by selenium in all its forms and attributed risk of harm to organisms and biodiversity resulting from selenium and its compounds (ECCC and Health Canada, 2017).

In response to numerous health risks, public health agencies have developed screening values for selenium in ambient water and fish potentially impacted by elevated selenium of geologic or anthropogenic origin. Consumption of selenium-contaminated fish is anticipated to supply a greater fraction of total allowable daily selenium intake, and screening values represent levels that, when detected, should trigger site-specific fish monitoring and advisories regarding recommended levels of consumption. Elevated selenium levels in aquatic species consumed by humans may adversely affect subsistence anglers (Beatty and Russo, 2014; ECCC and Health

Canada, 2017). Additional data may be useful to protect public health. Drinking water is anticipated to supply only a fraction of total allowable daily selenium intake, therefore public health agencies have established less stringent regulations or guidelines pertaining to drinking water standards. To decrease potential human health risks, further support for the creation of site- or watershed-specific thresholds and advisories may be warranted across the transboundary.

This report reviews the current state of knowledge for human health and selenium, with the following key findings:

1. Selenium is a required element for human health, and there is only a modest difference between selenium intake levels believed to promote human health and those associated with some acute or chronic effects. Thus, the typical protective “buffers” used to establish “safe” consumption levels for other toxicants (such as setting regulatory limits two orders of magnitude below the “no observed adverse effect level”) may not be available for selenium.
2. Human activities and natural geologic exposures can raise selenium levels in watersheds to a level that, when combined with common dietary exposures from other sources, may affect human health. This is especially true for persons engaging in subsistence fish (or aquatic plant) harvests. Preventing impacts from selenium due to mining and burning of coal and oil may require vigilant risk management procedures and hazard assessments based on water monitoring and achieving water quality goals.
3. Exposure levels in Canada and the United States are substantially affected by dietary supplement use. These must be factored into environmental exposure recommendations or use of the supplements themselves may have to be regulated or otherwise addressed in some fashion.
4. People relying on subsistence fish (and aquatic plant) harvests may have substantially higher selenium exposure than recreational fishers. This difference is accommodated in some national, state and provincial fish contamination limits. However, without interjurisdictional harmonization of these limits, it can lead to four different advisories on either side of an international watershed (US subsistence, US recreational, Canada subsistence and Canada recreational). This is confusing for public health messaging and enforcement.
5. Regulation of selenium pollution on either side of international or state/provincial borders may fail to account for sources on the other side. Maintaining selenium-safe watersheds may require an integrated approach to all sources in the watershed. Ideally, environmental, biomonitoring and human health data are shared and analyzed for the watershed as a whole.

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List of Acronyms and Units

ECCC	Environment and Climate Change Canada
g	gram
HPAB	Health Professionals Advisory Board
IJC	International Joint Commission
IOM	Institute of Medicine
kg	kilograms
L	Liter
mg	milligrams
mg/kg	dosage of substance (mg) based on body weight (kg)
mg/kg-d	dosage of substance (mg) based on body weight (kg) per day
nr	not reported
OEHHA	Office of Environmental Health Hazard Assessment (California)
ppb	Parts per billion = micrograms per Liter = microgram per kilogram
ppm	Parts per million = milligrams per Liter = milligrams per kilogram
Se	Selenium
UL	Tolerable Upper Intake Level
USEPA	US Environmental Protection Agency
WHO	World Health Organization
ww	Wet weight basis
µg	microgram

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1.0 Introduction

Selenium is an essential micronutrient for human health. Exposure and uptake occur predominantly through the diet. Selenium occupies a unique position in environmental public health because of the narrow margin between intake that is nutritionally sufficient and that which is hazardous (see **Table 1**). Studies conducted on human populations with overexposure to selenium from dietary sources have enabled the establishment of public health guidelines for selenium consumption to minimize the risk of “selenosis,” an overt condition primarily impacting the skin, hair and nails. A recent screening assessment by Environment and Climate Change Canada (ECCC) and Health Canada considered risk to human and environmental health posed by selenium in all its forms. This assessment attributed risk of harm to organisms and biodiversity resulting from selenium and its compounds (ECCC and Health Canada, 2017). Ongoing research also seeks to define beneficial or deleterious relationships between low selenium intake and chronic health conditions such as heart disease, diabetes and cancer.

2.0 Sources, Exposure and Pharmacology

Selenium in the natural environment occurs in numerous oxidative states that influence its physical, biochemical and toxicological characteristics. Selenium (Se_{34}^{79}) is a naturally occurring trace element found in the earth’s crust, basalt and in sulfide ores of metals (Canadian Council of Ministers of the Environment 2009; Malisa 2001). A trace element found in coal that can form both organic and inorganic compounds, selenium may reach levels up to 82 times its crustal concentration (Lussier et al. 2003). Selenium (Se) concentrations in raw coal are typically between 2 to 20 micrograms (μg) Selenium per gram (g) (Lemly 2003).

Selenium primarily enters the food web when inorganic selenate (+6) or selenite (+4) species are converted by microbes, algae and plants to organoselenium compounds. In dietary plants (e.g., cereals and vegetables) and meats, selenium is commonly encountered as selenomethionine and selenocysteine, amino acids in which the sulfur atom in methionine and cysteine is replaced by selenium (Raymond et al. 2008). An imidazole compound, selenoneine, was recently recognized as the major form of organoselenium present in fish and shellfish (Yamashita et al. 2013a). Other organoselenium compounds detected in fish include glutathione peroxidase (Brigelius-Flohé 1999; Rotruck et al. 1973), thioredoxin reductase (Mustacich and Powis, 2000) and selenoprotein (Burk and Hill, 1994).

Organoselenium compounds are the most common form humans consume through food (Miklavčič et al. 2013), while inorganic forms may be consumed through supplements or contaminants (Reilly 2006). Absorption of selenomethionine by active transport may exceed 95 percent and is greater than that of other organoselenium compounds, selenocysteine, and inorganic selenite and selenate. However, the absorption of selenocysteine, selenite and selenate also is relatively efficient (e.g., 50 to 80 percent) and of biological consequence (Reilly 2006).

Once absorbed, selenomethionine may randomly substitute for methionine in muscle and plasma proteins, the latter factor rendering it most efficient at increasing blood selenium levels. With regular exposure to selenomethionine, steady state blood selenium concentrations are reached in approximately one month (Fakih et al. 2006). Other forms of selenium, such as selenocysteine, selenate and selenite, are catabolized to selenide (-2), some of which is modified to an organic form and incorporated into specific selenoproteins, notably the important antioxidant enzyme glutathione peroxidase, and the carrier protein selenoprotein P, which transports selenium in plasma (Richardson 2005). Selenoneine has been reported in the blood of fish consumers at high concentrations that depend on the frequency of fish consumption (Yamashita et al. 2013b). Selenium is excreted predominantly in the urine as various selenosugars (Lajin et al. 2016) that may be from the diet, e.g., muscle of marine fish (Kroepfl et al. 2015). At high levels of selenium intake associated with selenosis (see below), minor amounts of selenium may be expired as dimethyl selenide, which imparts a garlic odor to the breath (National Institutes of Health 2016).

Food (including supplements) is the primary source of daily selenium intake for the general population, accounting for 99 percent of uptake. Organ meat and seafood generally contain the highest concentrations (0.4 to 1.5 $\mu\text{g/g}$), followed by skeletal muscle meat (0.1 to 0.4 $\mu\text{g/g}$), and grains, nuts and cereals (0.1 to 0.8 $\mu\text{g/g}$) (Rayman 2008). With a few notable exceptions, such as Brazil nuts, fruits and vegetables contain relatively little selenium (National Institutes of Health 2016). Selenomethionine and sodium selenite are common constituents of multivitamins at 50 to 100 μg per tablet, and specific selenium supplements may contain 100 to 200 μg per tablet. According the 2011-2012 National Health and Nutrition Examination Survey, the average daily selenium intake in Americans aged two years and older from foods is 111 μg and from both foods and supplements is 130 μg (USDA 2014). Based on the 2004 Canadian Community Health Survey, it was estimated that the median dietary selenium intake in adults ranged from 83 to 151 $\mu\text{g/day}$, with a 95th percentile intake as high as 236 $\mu\text{g/day}$ (ECCC and Health Canada, 2017).

Certain subgroups of the population may be at risk of selenium consumption in excess of recommended limits (discussed further below) if they engage in frequent, if not exclusive, consumption of grains and vegetables harvested from highly seleniferous soils or fish caught in aquatic environments subject to selenium contamination. Selenium bioaccumulates in the aquatic environment and fish living in waters subject to emissions or runoff from coal and metal mining, metal smelting and refining, and agricultural irrigation drainage may have elevated selenium content. It was estimated that total selenium intake could exceed 600 $\mu\text{g/day}$ for First Nation residents eating fish at the 95th percentile consumption level in the Elk Valley watershed of British Columbia that was most contaminated from coal mining (Lawrence and Chapman, 2007). Inuit communities in northern Canada whose traditional diet includes seals and Beluga whales that bioaccumulate naturally occurring selenium may ingest less than 600 $\mu\text{g Se/day}$ at $\geq 90^{\text{th}}$ percentile consumption levels (Laird et al. 2013).

High selenium levels can accumulate in the ecosystem via leaching from industrial activities, mining waste and anthropogenic emissions from the burning of coal (Lemly 2003). Other industrial uses of selenium compounds that could potentially be associated with occupational exposure include metallurgy, glass manufacturing, chemical and pigments, electronic components and animal feed additives (Anderson 2015). Industrial and mining-related operations account for nearly 40 percent of the selenium emissions into atmospheric and aquatic

environments (Tan et al. 2016). Public drinking water supplies in Canada and the United States generally contain less than 2 µg per Liter (L), and therefore contribute little to dietary intake (ECCC and Health Canada, 2017; OEHHA 2010). However, cases of excessive selenium exposure from well water contaminated by mining operations have been reported (ECCC and Health Canada, 2017; OEHHA 2010). Finally, selenium sulfide is often used in shampoos and topical medications for treatment of seborrheic dermatitis and other skin conditions but absorption through the skin is negligible.

Aquatic ecosystems and aquatic-dependent vertebrates are extremely sensitive to selenium-laden water. Egg-laying vertebrates can have high levels of embryo mortality, while fish can suffer larva deformities (Tan et al. 2016). Natural selenium concentrations in aquatic systems often are not high enough to be toxic to ecosystem inhabitants (Ogle and Knight, 1996). However, ambient water concentrations of just 5 to 10 µg/L of selenium can rapidly bioaccumulate, causing toxicity in the food web. Bioaccumulation of selenium in contaminated sediments can be cycled into food webs for decades (Lemly 2002). Initial selenium toxicity in adult fish often can go undetected while successful reproduction is interrupted or fails (Coyle et al. 1993). Maternal transfer, where high selenium concentrations are received by eggs from Se-exposed females, is a well-documented pathway for selenium exposure (Janz et al. 2010). When the eggs hatch, selenium is then metabolized by the developing fish (Lemly 2002).

Environmental impacts from mining can be devastating and long lasting even after rehabilitation and reclamation (Mkpuma et al. 2015). For example, poor practices and industrial activities have released toxic amounts of selenium into the environment, which can decimate wildlife populations. This impact was shown in the 1970s North Carolina Belews Lake, where entire populations of reservoir fish were eliminated and long-term impacts to the ecosystem were observed because of power plant waste discharges containing high amounts of selenium (Lemly 2002). Widespread impacts—due to elevated selenium concentrations—on sensitive ecosystems and human health within the Crown of the Continent region will compound as industrial and mining operations expand (British Columbia Auditor General 2016; Hauer et al. 2007). Ongoing studies of water and biota characterize impacts from a history of coal mining activity in the Elk River basin of southeastern British Columbia (Kinneer 2012), including long-term increases in selenium concentrations over time in water downstream of the Elk Valley River coal mines (Chapman et al. 2010; Hauer and Sexton, 2013). The Elk River flows into the Kootenai River and has impacts on downstream US waters. Recent monitoring efforts by a partnership of US state, federal and tribal agencies confirm increases in selenium concentrations over time in water and fish tissue downstream and to the south of the Elk Valley River coal mines in Lake Koocanusa (Mebane and Schmidt, 2019).

It may further negatively impact human health when ordinary dietary exposures of selenium are combined with sources from human activities (Gottlieb et al. 2010). Selenium contamination in aquatic ecosystems can cause a cascade of bioaccumulation events which often can extend the timeframe for intervention and restoration efforts over many years (Chapman 1996). Preventing impacts from selenium due to mining and fossil fuel burning may require vigilant risk management procedures and hazard assessments based on water monitoring and achieving water quality goals to assist in averting threats to the ecosystem and human health (Lemly 2003).

Whole blood selenium is considered the most useful biomarker of intermediate to long-term selenium exposure (Hays et al. 2014; Noisel et al. 2014). In the 2011 to 2012 cycle of the US National Health and Nutrition Evaluation Survey, representative values for selenium in whole blood for the US population were 190 µg/L (geometric mean), 190 µg/L (50th percentile) and 236 µg/L (95th percentile) (National Center for Environmental Health 2015). Corresponding values reported in the Canadian Health Measures Survey cycle I (2007 to 2009) were 202, 200, and 253 µg/L (Health Canada 2010).

3.0 Selenium Exposure Guidelines

Selenium is an essential element in human nutrition. It plays a role in the function of numerous proteins (selenoproteins) and enzymes, particularly those involved in redox regulation and pathways, thyroid hormone action, immune response and inflammation. However, as previously noted, there appears to be a very modest difference between levels necessary for these healthy functions and levels associated with acute or chronic health effects. Of all trace elements, selenium has the narrowest margin between intake—which is required for human nutritional needs—and that which is hazardous to health (Beatty and Russo, 2014).

Although some experimental studies indicate that inorganic selenium exerts greater toxicity than organoselenium following acute or subacute high dose ingestion, uncertainties remain regarding the differential toxicity of selenium species following long term dietary exposure, and current intake guidelines apply equally to all chemical forms (Raymond et al. 2008). Selenium intake guidance also has been developed without adjustment for the potential presence of other dietary metals and metalloids with which selenium may interact (see **Section 6**).

A summary of nutritional guidelines is shown in **Table 1** (next page). In a report sponsored in part by the US Department of Health and Human Services and Health Canada, the Food and Nutrition Board at the Institute of Medicine of the National Academies (IOM 2000) established a Recommended Dietary Allowance for selenium in adults of 55 µg/day (20 µg/day in children age one to three years). The Recommended Dietary Allowance—the average daily level of intake considered sufficient to meet the nutrient requirements of nearly all (97 percent to 98 percent) healthy individuals—was based on intake associated with a maximal (or plateau) plasma concentration of the selenium dependent enzyme glutathione peroxidase. An analogous parameter established by the World Health Organization (WHO), termed the Recommended Nutrient Intake, was set at 26 µg/day for females and 34 µg/day for males between 19 and 65 years of age (WHO 2004). The Recommended Nutrient Intake was based on a selenium intake considered sufficient to maintain plasma glutathione peroxidase at two-thirds of maximal concentration. Substantial uncertainty exists regarding the impact, beneficial or deleterious, of maximizing selenoprotein levels or enzymatic activity (Jablonska and Vinceti, 2015). The proposed protection provided by selenium against cancer and chronic disease was not supported by randomized trials of supplementation. Rather, recent biochemical studies indicate that selenium overexposure may result in a range of toxic impacts, including oxidative stress and the

consequent exhaustion of antioxidant enzymes in response to this oxidative activity. This adverse response may appear at lower concentrations than expected.

Table 1. Summary of reported nutritional guidelines. nr = not reported.

Nutritional Criteria		World Health Organization (WHO)	Institute of Medicine National Academies (IOM)
Daily nutrition	Adults	26 µg/day females ^{1 ^} 34 µg/day males ^{1 ^}	55 µg/day ^{2 +}
	Children	nr	20 µg/day ^{2 +}
Tolerable Upper Intake Level (UL)	Adults	nr	400 µg/day ²
	Children	nr	90 µg/day ²

1 WHO 2004

2 IOM 2000

+ Recommended Dietary Allowance

^ Recommended Nutrient Intake

The Institute of Medicine (IOM 2000) established a Tolerable Upper Intake Level (UL) for selenium in adults of 400 µg/day (90 µg/day for children age one to three years) by applying an uncertainty factor of two to a “no observed adverse effect level” of 800 µg/day observed in the Enshi County, China selenosis outbreak (see **Section 4.2**). The UL is defined as the highest level of nutrient intake (from food and supplements) that is “likely to pose no risk of adverse health effects in almost all individuals” (IOM 2000). Based on similar data from Enshi, but applying slightly different “no observed adverse effect levels” and uncertainty factors, the US Environmental Protection Agency (USEPA) established a “Reference Dose” and the US Agency for Toxic Substances and Disease Registry established a “Minimal Risk Level” for oral selenium intake of 5 µg per kilograms (kg) per day (µg/kg-d). The “Reference Dose” and the “Minimal Risk Level” equate to oral selenium intake of 350 µg/day in a 70 kg adult. The Biomonitoring Equivalents in whole blood corresponding to the UL “Reference Dose” and “Minimal Risk Level” in adults are 480 µg/L, 400 µg/L, and 400 µg/L respectively (Hays et al. 2014).

Drinking water, ambient water and fish tissue guidelines are shown in **Table 2**. Because drinking water is anticipated to supply a fraction of total allowable daily intake, public health agencies have established regulations or guidelines pertaining to selenium in drinking water. These include the USEPA maximum contaminant level for selenium in drinking water of 50 µg/L (USEPA 2015); Health Canada maximum acceptable concentration of 50 µg/L (Health Canada 2014); the WHO provisional guideline value of 40 µg/L (WHO 2011); and the State of California public health goal of 30 µg/L (OEHHA 2010).

Public health agencies also have developed screening values for selenium in fish potentially impacted by elevated selenium of geologic or anthropogenic origin, as elevated selenium levels

in aquatic species consumed by humans may adversely affect subsistence anglers (Beatty and Russo, 2014; ECCC and Health Canada, 2017). The screening values—which may vary in part based on whether the consumer is a recreational or subsistence fisher—represent levels that should trigger site-specific fish monitoring and advisories regarding recommended levels of consumption. The USEPA (2000) developed a selenium screening value in fish tissue of 20.0 parts per million (ppm) wet weight (ww) applicable to recreational fishers (average consumption rate of 17.5 gram per day), and 2.457 ppm ww for adult subsistence fishers (average consumption of 142.4 gram per day). More recently, assuming a fish consumption rate of 54 grams per day by adults, a fish selenium screening value of 7.7 ppm was advised (USEPA 2016a). This screening value will vary at different intake rates (USEPA 2016a). California’s Office of Environmental Health Hazard Assessment (OEHHA 2008) derived a fish contaminant goal for selenium of 7.4 ppm ww for adult recreational fishers. The British Columbia Ministry of Environment and Climate Change Strategy developed fish screening values for selenium of 1.8 ppm ww and 18.7 ppm ww applicable to high fish consumers (average of 220 g/day) and low fish consumers (average of 21.5 g/day) respectively (British Columbia Ministry of Environment and Climate Change Strategy 2020).

Table 2. Summary of reported drinking water, ambient water and fish tissue guidelines. nr = not reported; ww = wet weight.

	Drinking Water Criteria	Ambient Water Quality Criteria		Screening Values in Fish Tissue	
		Lentic Waters	Lotic Waters		
WHO	40 µg/L ^{3 *}	nr	nr	nr	nr
Health Canada	50 µg/L ^{4 **}	nr	nr	nr	nr
USEPA	50 µg/L ^{5 ***}	1.5 µg/L ⁶	3.1 µg/L ⁶	20.0 ppm ww ^{7 a}	2.457 ppm ww ^{7 b}
Alberta	50 µg/L ^{8 **}	nr	nr	nr	nr
British Columbia	10 µg/L ^{9 ***}	2 µg/L ⁹	2 µg/L ⁹	18.7 ppm ww ^{9 c}	1.8 ppm ww ^{9 d}
California	30 µg/L ^{10 ****}	nr	nr	7.4 ppm ww ^{11 e}	nr
Idaho	50 µg/L ^{12 ***}	nr	nr	nr	nr
Manitoba	10 µg/L ^{13 **}	nr	nr	nr	nr
Michigan	50 µg/L ^{14 ***}	nr	nr	nr	nr
Minnesota	30 µg/L ^{15 ***}	nr	nr	nr	nr
Montana	50 µg/L ^{16 ***}	nr	nr	nr	nr
North Dakota	50 µg/L ^{17 ***}	nr	nr	nr	nr
Ontario	50 µg/L ^{18 **}	nr	nr	nr	nr
Saskatchewan	50 µg/L ^{19 **}	nr	nr	nr	nr
Washington State	50 µg/L ^{20 ***}	nr	nr	nr	nr

3 WHO 2011
 4 Health Canada 2014
 5 USEPA 2015
 6 USEPA 2016b
 7 USEPA 2000
 8 Government of Alberta 2018

9 British Columbia Ministry of the Environment and Climate Change Strategy 2020
 10 OEHA 2010
 11 OEHA 2008
 12 Idaho Department of Environmental Quality 2019

13 Manitoba Water Stewardship 2011
 14 Michigan Department of Environment, Great Lakes, and Energy 2019
 15 Minnesota Department of Health 2019

16 Montana Department of Environmental Quality 2019
 17 North Dakota Legislature 2001
 18 Government of Ontario 2017
 19 Water Security Agency 2015
 20 Washington Legislature 2019

* Provisional Guideline
 ** Maximum acceptable concentration
 *** Maximum contaminant level
 **** Public Health Goal

a Recreational fishers
 b Adult subsistence fishers
 c Low fish consumers
 d High fish consumers
 e Fish contaminant goal for adult recreational fishers

In 2016, the USEPA issued an “aquatic life ambient water quality criterion” for selenium intended to be protective of the viability of freshwater fish populations (USEPA 2016b) to help protect subsistence or recreational harvests. To meet the fish tissue criterion, chronically exposed fish should have a muscle selenium concentration of less than 11 ppm (dry weight). The corresponding limits for selenium in water were 1.5 µg/L, or parts per billion (ppb) (lentic waters), and 3.1 µg/L, or ppb (lotic waters), respectively (see **Table 2** above). The term lentic describes still waters, and lotic references actively moving waters. The occurrence of selenium in aquatic systems is attributed to local geology and mining activity (Chapman et al. 2010). British Columbia ambient water guidelines are 2 µg/L (British Columbia Ministry of Environment and Climate Change Strategy 2020). Levels of selenium in waters shared by Canada and the United States tend to fall below current guidelines for drinking water in both countries, though some exceedances have been reported (**Table 3**, next page).

One such example involves elevated selenium levels in the Kootenai River downstream of the Elk River, spanning the border of Canada (British Columbia) and the United States (Montana and Idaho). To address this issue, recent work further south in the Lake Koocanusa ecosystem aims to identify water quality standards for selenium levels in the lake to protect sensitive fish and other aquatic species (Jenni et al. 2017), and is supported by Montana's Department of Environmental Quality and British Columbia's Ministry of the Environment and Climate Change Strategy, through a multistakeholder Monitoring and Research Working Group. The Monitoring and Research Working Group also supports Montana's ongoing review of its water quality and fish tissue standards. While Montana and Idaho adopted USEPA's standards statewide, Montana also aims to develop additional site-specific water and fish tissue standards for the Libby Dam area.

To date, no long-term studies of selenium intake in residents of the affected watershed, with different aquatic consumption patterns downstream from Elk Valley coal mines have been performed. Additional data may be useful to protect public health. To decrease potential human health risks, and per the example of Montana, further support for the creation of site- or watershed-specific selenium thresholds and advisories may be warranted across the transboundary.

While the governments of Canada and the United States have worked to address the health risks posed by elevated selenium in aquatic systems within their borders, connecting these efforts for shared watershed systems along the border remains a challenge. For instance, minimizing the surface disposal of mine waste and wastewater, and using practices like the backfilling of solids or *in situ* water recycling, can reduce the potential of cross-border selenium transport in the environment (Lemly 2003). Treating transboundary watersheds as a unit would ensure appropriate source controls and human health advisories regardless of location in the watershed. Efforts to routinely monitor health and ecological data in transboundary aquatic systems at risk for selenium contamination would increase public health protection in both countries. Programs supporting more routine selenium monitoring and reporting for water and fish in shared watersheds also should include provisions for routine sharing of health, ecological and environmental data between the two countries.

Table 3. Reported selenium (Se) levels in select Canada-US transboundary watersheds. nr = not reported.

Year		2017	2014	2013	2012	2011	2010	2009	2008	2007	2006	2001	1985	1975	1974	1973
Transboundary Basins																
St. Croix River Basin^b	# of Samples	10	10	12	8	4	14	20	nr							
	Min (µg/L)	<0.03	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	nr						
	Max (µg/L)	0.07	<0.1	<0.1	<0.1	<0.1	<0.1	0.2	0.1	nr						
Souris River Basin^c	# of Samples	16	16	16	18	19	13	18	14	16	18	nr	nr	nr	nr	nr
	Min (µg/L)	.036	.33	0.33	0.3	0.3	0.27	0.24	0.47	0.26	0.22	nr	nr	nr	nr	nr
	Max (µg/L)	1.2	.73	2.36	0.69	0.7	0.65	1.61	1.81	0.79	0.61	nr	nr	nr	nr	nr
Red River Basin Aquifers^d	# of Samples	46	nr	144	nr	nr	nr	nr								
	Median (µg/L)	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	1.7	nr	nr	nr	nr
	Max (µg/L)	1.9	nr	21	nr	nr	nr	nr								
Rainy River Basin Aquifers^d	# of Samples	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	39	nr	nr	nr	nr
	Median (µg/L)	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	1.4	nr	nr	nr	nr
	Max (µg/L)	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	308	nr	nr	nr	nr
Great Lakes Basin																
Lake Superior Basin^d	# of Samples	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	56	nr	nr	nr	nr
	Median (µg/L)	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	1.2	nr	nr	nr	nr
	Max (µg/L)	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	93	nr	nr	nr	nr
Lake Ontario^e	# of Samples	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr
	Median (µg/L)	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	0.97	nr	nr	nr
	Max (µg/L)	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	1.9	nr	nr	nr
Lake Erie (western)^f	# of Samples	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	6	6	12
	Mean (µg/L)	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	2	1	4
	Max (µg/L)	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr
Canada/ US Drinking Water Guidelines for Se^a	50 µg/L															

a. USEPA 2015 and Health Canada 2014

b. Data comes from the available annual reports of the International St. Croix River Watershed Board between the years 2008 to 2018, reports accessed at: ijc.org/en/scrwb/library/reports, June 10, 2020.

c. Data comes from the available annual reports of the International Souris River Board between the years 2006 to 2018, reports accessed at: ijc.org/en/srb/library/reports, June 10, 2020.

d. Minnesota Pollution Control Agency 2001

e. Rossman and Barres, 1987

f. Adams and Johnson, 1977

4.0 Clinical Toxicology: Case Study Examples

Clinical characteristics of human intoxication from subacute and chronic overexposure to selenium, a condition termed “selenosis,” are described in two episodes of mass overexposure involving over 100 people per episode. The toxicological mechanism(s) underlying selenosis is uncertain but may involve selenium interaction with protein thiols and structural disruption of macromolecules including enzymes.

4.1. Subacute selenium intoxication from misformulated dietary supplement: USA, 2008

Beginning in March 2008, the US Food and Drug Administration announced the voluntary recall of approximately 1200 bottles of a liquid dietary supplement known as “Total Body Formula” and “Total Body Mega Formula” that were linked to subacute selenium intoxication in dozens of individuals in ten states. Due to a manufacturing error, a daily one-ounce serving of the supplement contained up to 40,800 μg of selenium, instead of the 200 μg intended (e.g., approximately 200-fold excess). Subsequent analysis of multiple lots found most to contain approximately 25,000 μg selenium per one-ounce dose in a form consistent with sodium selenate (Morris and Crane, 2013).

According to a US Centers for Disease Control and Prevention report on 201 confirmed cases, the most frequently reported symptoms included diarrhea (78 percent), fatigue (72 percent), hair loss (70 percent), joint pain (67 percent), nail discoloration or brittleness (61 percent), nausea (57 percent) headache (45 percent) and tingling in the extremities (39 percent) (MacFarquhar et al. 2010). The proportion of scalp hair lost ranged from 10 to 100 percent, with a median of 50 percent. Eighteen percent of the subjects reported complete loss of scalp hair. Some individuals experienced complete loss of multiple fingernails or toenails (Morris and Crane, 2013). Most subjects experienced the onset of symptoms within ten days. The median period of consumption was 29 days (range of one to 109 days). Based on a content of 40,800 selenium per ounce, the median estimated selenium ingestion during the episode was 989 milligrams (mg) (range 41 to 5875 mg, $n = 156$), or 12.8 mg/kg (range 0.5 to 115.4 mg/kg, $n = 98$). Follow-up questionnaires and interviews available on 30 to 40 percent of the subjects at 90 or more days after cessation of product use found that 52 percent (32 of 62) reported persistent fingernail discoloration, brittleness or loss, 35 percent (22 of 63) persistent fatigue, and 29 percent (16 of 56) persistent hair loss. Less than 25 percent of subjects reported persistent joint or muscle pain, or tingling. Peripheral nerve dysfunction was not evaluated by objective neurophysiological testing. Nine symptomatic patients evaluated in a medical toxicology clinic had whole blood selenium collected a median of 14 days post cessation of exposure (range seven to 118 days). The median whole blood selenium concentration was 318 $\mu\text{g/L}$ (range 150 to 732 $\mu\text{g/L}$). A separate study following exposure to these supplements reported that most of the patients experienced significant resolution of symptoms (alopecia, dystrophic fingernail changes, gastrointestinal symptoms and memory difficulties) by four weeks post cessation (Aldosary et al. 2012).

4.2. Chronic selenium intoxication from high selenium food: Enshi China, 1960s

In the early 1960s, over 100 people in five rural villages in Enshi County, China were affected by an illness predominantly characterized by hair and nail loss (Yang et al. 1983; Yang et al. 1989; Yang and Zhou, 1994; Yang and Xia, 1995). Clinical and epidemiological investigation established the cause to be chronic overexposure to selenium, mainly from consumption of vegetables and grain containing elevated levels of selenomethionine associated with growth on highly seleniferous soil. The residential practice of roasting corn and other foods over local coal with high selenium content may also have contributed to ingestion and inhalation of inorganic selenium.

The outbreak coincided with a drought that caused failure of the rice crop, forcing the villagers to increase consumption of high-selenium vegetables and corn. Affected individuals initially experienced dry and brittle head hair that easily broke off, particularly by scratching a pruritic rash on the scalp. New hair growth exhibited decreased pigment and luster. Hair loss sometimes affected the face and trunk. Subsequent to hair loss, nails became brittle, with white spots and streaks on the surface. Thickening, cracking, and breakage of fingernails often ensued, ultimately with sloughing of the nail and growth of a deformed replacement. In advanced cases toenails were affected. Exudative paronychia commonly occurred. Additional cutaneous findings included redness, swelling, blistering and ulceration of the limbs and the back of the neck. Three of 18 patients residing in the most heavily affected village complained of peripheral paresthesias and gastrointestinal disturbances (Yang et al. 1983).

At the peak of the Enshi outbreak from 1961 to 1964, average dietary selenium intake was estimated to be 15,000 to 38,000 μg per day, or in terms of dosage, 0.27 to 0.69 $\text{mg}/\text{kg}\cdot\text{d}$. In the following decade, when local corn consumption declined but cases of selenosis occasionally still occurred, selenium intake was estimated to average 4990 $\mu\text{g}/\text{d}$ (range 3200 to 6990). At that time, a survey of residents in the endemic area revealed a mean blood selenium concentration of 3200 $\mu\text{g}/\text{L}$ (range 1300 to 7500, $n = 72$) (Yang et al. 1983). Among 349 residents, only one patient with selenosis had a blood selenium concentration less than 1000 $\mu\text{g}/\text{L}$. Selenosis was present in 30 percent of individuals with a blood selenium between 1000 to 3300 $\mu\text{g}/\text{L}$ (Yang and Xia, 1995). Interestingly, no selenosis occurred in individuals under the age of 12 years, suggesting that overt clinical findings may require many years of exposure at that dose level. Patient medical evaluations indicated that observed fingernail lesions resolved in affected individuals when dietary selenium consumption declined to 800 $\mu\text{g}/\text{d}$ (0.015 $\text{mg}/\text{kg}\cdot\text{d}$).

5.0 Potential Health Protection and Risks

Numerous epidemiological studies in large adult population cohorts in North America and Europe have examined the association of selenium status and supplementation with the risk of cancer and chronic disease. Researchers have considered selenium's potential to confer protection from some forms of cancer, and a recent Cochrane systematic review and meta-analysis noted an inverse association between selenium status (as measured by dietary assessment or levels in blood or toenails) and certain cancers in observational studies (Vinceti et al. 2018). However, the relationship was demonstrated predominantly in men and not women, and the role of confounding and other bias could not be ruled out. Upon reviewing randomized clinical trials for comparison, the authors did not find evidence for a protective effect of selenium supplementation in reducing cancer risk.

Recent studies have raised concern of an association between selenium supplementation and the risk of prostate cancer (Kenfield et al. 2014; Kristal et al. 2014), though the findings for this potential association have been mixed. For instance, the study by Kenfield et al. (2014) found an association between high selenium exposure (140 or more $\mu\text{g}/\text{day}$) and mortality from prostate cancer in men previously diagnosed with prostate cancer. The Cochrane review referenced above (Vinceti et al. 2018) found that in studies of low bias there was no effect of selenium on prostate cancer risk. Studies in rodents indicated potential carcinogenicity for two selenium compounds, selenium sulfide and ethyl selenac (selenium diethyldithiocarbamate), though the US Agency for Toxic Substances and Disease Registry considers significant human intake of these forms of selenium unlikely (ATSDR 2003). Moreover, populations with high chronic Se exposure through consumption of whales and seafood such as Inuit in Greenland (Hansen et al. 2004) and residents of whale consuming communities in Japan (Nakamura et al. 2014), showed no recorded clinical signs or no observable adverse effects.

When considering potential association with chronic impacts and diseases, there is significant epidemiologic evidence that acute selenium exposure can result in neurotoxicity in humans, including symptoms such as lethargy, dizziness, motor weakness and burning/prickling in extremities (paresthesias). Moreover, some support exists for similar impacts resulting from low-level chronic selenium overexposure. In addition to the above noted neurotoxicity, the authors also found an association between amyotrophic lateral sclerosis and Se exposure reported among individuals in Italy with high selenium intake (Vinceti et al. 2014).

A recent Cochrane systematic review and meta-analysis found no impact of selenium supplementation on the risk of cardiovascular disease (Rees et al. 2013), though there is evidence for positive effects between whole blood Se and the prevalence of stroke in representative samples of the Canadian and the US population (Hu et al. 2019). The relationship between selenium status and selenium supplementation and the risk of diabetes mellitus is uncertain, due to inconclusive, borderline and sometimes conflicting epidemiological findings and biochemical effects (Mao et al. 2014; Rayman and Stranges, 2013). Selenium has not been determined to cause adverse reproductive outcomes in humans, and doses causing adverse reproductive effects in animals have been approximately five-fold higher than those associated with emergence of overt human selenosis (Cukierski et al. 1989; ECCC and Health Canada, 2017). However,

selenium can bioaccumulate in the aquatic food chain and cause toxicity in fish. For example, a fish egg receives selenium from the female's diet and stores it until hatching, whereupon it is metabolized by the developing fish. If concentrations in eggs are great enough (about 10 µg/g or greater), biochemical functions may be disrupted, and teratogenic deformity and death may occur (Lemly 2002).

6.0 Selenium Interactions with Metalloids and Metals: Arsenic and Mercury

The health impacts from compounds formed by interactions between selenium and arsenic, or selenium and mercury, also has attracted significant interest and attention from researchers. The interactions between selenium and arsenic or mercury may be influenced by the formation of metal complexes with inorganic or organoselenium compounds, the activity of related metabolic pathways (e.g., biomethylation in the case of arsenic) or the antioxidant role of selenoenzymes in the mitigation of metal-induced oxidative stress. Animal experiments have demonstrated that arsenic and selenium interact to form a seleno-bis (S-glutathionyl) arsinium ion, $(GS)_2AsSe^-$, that is secreted in bile (Gailer 2009). The implication of this interaction is uncertain, as both antagonistic and synergistic effects on toxicity (including carcinogenicity) of arsenic and selenium have been observed in *in vitro* and *in vivo* experimental models (Sun et al. 2014). In epidemiological studies of populations with elevated arsenic exposure, low levels of plasma or serum selenium have been associated with reduced efficiency of arsenic methylation (Basu et al. 2011; Pilsner et al. 2011), a recognized risk factor for arsenic-induced chronic health effects.

Inorganic selenium and organoselenium compounds react with mercury to form insoluble complexes *in vivo*, and animal studies have observed the capacity of selenium to antagonize or ameliorate the developmental and adult neurotoxicity of methylmercury (Beyrouy and Chan, 2006; Heath et al. 2010; Ralston and Raymond, 2010). The ability of dietary selenium to mitigate the toxicity of methylmercury in humans is uncertain. In prospective birth cohort studies conducted in Faroe Island (Denmark) communities with elevated dietary methylmercury and sufficient dietary selenium, no significant protective effects of selenium on methylmercury induced developmental toxicity were apparent (Choi et al. 2008). Among adult residents of the Brazilian Amazon with relatively high dietary methylmercury and a wide range of dietary and plasma selenium, a positive association between blood mercury and age-related cataract was observed only among those with low plasma selenium (Lemire et al. 2010).

It has been suggested that the risk of methylmercury ingestion from fish is reduced in species that have a high molar ratio of selenium to mercury in edible flesh, and that indices based on absolute and relative amounts of methylmercury and selenium should govern dietary fish advisories (Ralston et al. 2016). For example, the Chippewa Ottawa Resource Authority monitors fish contaminants in Anishinaabe (Great Lake Native American) tribal fisheries, including methylmercury and polychlorinated biphenyls, two toxic substances that are the primary contributors to consumption advisory limits for these fish. A recent report on this fishery

(Dellinger et al. 2018) includes a selenium benefit metric to characterize the possible protective value against methylmercury neurotoxicity. Congruent with Anishinaabe cultural motivations to consume fish from their ancestral fisheries, nutritional content was high in locally caught fish and, in some respects, superior to farmed/store-bought fish. These Great Lakes fish still contained levels of polychlorinated biphenyls that require careful education and guidance for consumers. However, the contaminant trends suggest that these fish need not be abandoned as important (both culturally and nutritionally) food sources for the Anishinaabe who harvested them.

Others have noted that the considerable variability in selenium to mercury ratios associated with fish size, temporal trends and geographic factors—even within the same fish species—effectively limits the value of such ratios in risk assessment or dietary guidance (Burger and Gochfeld, 2012; Burger et al. 2012). Nevertheless, evidence suggests that selenium significantly impacts the toxicology of mercury and that future risk assessments of mercury exposure or selenium intake should consider the interactions between the two compounds (Zhang et al. 2014).

7.0 Summary

This report reviews the current state of knowledge for human health and selenium, with the following key findings.

1. Selenium is a required element for human health, and there is only a modest difference between selenium intake levels believed to promote human health and those associated with some acute or chronic effects. Thus, the typical protective “buffers” used to establish “safe” consumption levels for other toxicants (such as setting regulatory limits two orders of magnitude below the “no observed adverse effect level”) may not be available for selenium.
2. Human activities and natural geologic exposures can raise selenium levels in watersheds to a level that, when combined with common dietary exposures from other sources, may affect human health. This is especially true for persons engaging in subsistence fish (or aquatic plant) harvests. Preventing impacts from selenium due to mining and burning of coal and oil may require vigilant risk management procedures and hazard assessments based on water monitoring and achieving water quality goals.
3. Exposure levels in Canada and the United States are substantially affected by dietary supplement use. These must be factored into environmental exposure recommendations or use of the supplements themselves may have to be regulated or otherwise addressed in some fashion.
4. People relying on subsistence fish (and aquatic plant) harvests may have substantially higher selenium exposure than recreational fishers. This difference is accommodated in some national, state and provincial fish contamination limits. However, without interjurisdictional harmonization of these limits, it can lead to four different advisories on either side of an international watershed (US subsistence, US recreational, Canada subsistence and Canada recreational). This is confusing for public health messaging and enforcement.
5. Regulation of selenium pollution on either side of international or state/provincial borders may fail to account for sources on the other side. Maintaining selenium-safe watersheds may require an integrated approach to all sources in the watershed. Ideally, environmental, biomonitoring and human health data are shared and analyzed for the watershed as a whole.

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