



# Potential Human Health Impacts Related to Selenium in Fish from the North Saskatchewan River

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## 1.0 Introduction

Selenium is a naturally occurring element that is an essential micronutrient in human and animal nutrition (Chen et al. 2006; ATSDR 2003; Goldhaber 2003). It may be released as a result of the weathering of rocks or from volcanic emissions, and be present in air, water, soil or plants. Anthropogenic sources of selenium, defined as sources related to human activities, also include mining, milling, refining (specifically copper) and oil and gas operations (ATSDR 2003).

Shell Canada recently commissioned a series of studies on the concentrations of selenium in water, fish tissue, benthic invertebrates and sediments in the North Saskatchewan River (NSR) in the vicinity of its Scotford Complex. The studies were conducted by Stantec and North/South Consultants in 2007 and 2008 and focused on the levels of selenium in the abiotic and biotic environment of the NSR (Stantec 2008a/b; North/South 2008 a/b). A subsequent technical memorandum by Golder Associates offered an interpretative assessment of the potential aquatic impacts of the measured selenium concentrations in the NSR (Golder Associates Ltd. 2008). These studies did not, however, address the potential impacts that measured selenium levels in fish may pose to the health of the area residents who eat these fish.

The following analysis provides an assessment of the potential impacts of selenium to human health as a result of the consumption of fish from the NSR, based on the results of the studies noted. This analysis serves as a response to the Supplemental Information Request received from Alberta Environment on January 27, 2009. The actual characterization of the potential impacts to human health is followed by a general discussion on the importance of selenium in normal physiologic function, with an overview of the potential for exposure, pharmacokinetics and toxicity of selenium provided in Appendix A.

## 2.0 Measured Selenium Concentrations

The survey and analysis of fish selenium concentrations was conducted by North/South in 2007 and 2008 (North/South 2008a,b).

The North/South study team attempted to target fish species from three different trophic levels in their survey, including:

- Small, sedentary fish, which prey on small benthic invertebrates. The target species was a small minnow, longnose dace (*Rhinichthys cataractae*);
- A large-bodied benthic feeding fish, which also preys on benthic invertebrates. The target species was white sucker (*Catostomus commersoni*);
- Highly mobile top predators in the aquatic food web such as walleye (*Sander vitreus*), which feed on fish and aquatic insects.

An insufficient number of walleye were captured to allow for selenium analysis. Instead, tissue samples were collected from white sucker and longnose dace in 2007 (reported in 2008a). Although bottom-dwelling fish like white sucker are not commonly eaten, they can still be used to assess the potential human health impacts related to selenium. A study uniquely identifying selenium concentrations in fish found higher concentrations (statistically significant) in lower trophic-level species when compared to higher trophic-level species (Burger et al. 2001). Selenium levels were found to be highest in non-migratory sediment feeding (or bottom-dwelling) species (e.g., white sucker) when compared to higher trophic-level, migratory species in the water column (e.g., walleye). The fish with the highest selenium levels maintained a diet of mainly benthic invertebrates, as is typical for white sucker.

In the 2007 study, as noted by North/South (2008a), longnose dace and white suckers were collected in the vicinity of the Scotford Complex. A total of eight composite samples of longnose dace, each composed of three fish, were collected from three sampling areas. A total of sixteen female white suckers were collected: eight from an area upstream of the Shell Scotford Complex outfall and eight from an area downstream of the same outfall. White suckers were analyzed for selenium in muscle, ovaries and whole body. As large-bodied fish may move regularly between the upstream and downstream areas, North/South (2008a) acknowledged that white suckers captured from the two areas may represent the same populations. For the purpose of the health impact assessment, these data were considered to be characteristic of a single white sucker population. As such, no distinction was made between the upstream and downstream concentrations of selenium in fish.

In the subsequent 2008 sampling program described in North/South (2008b), eight composite samples of longnose dace were collected from five sampling areas while a total of sixteen white suckers were once again collected from areas upstream and downstream of the outfall. This time, selenium levels in white suckers were only measured as whole body concentrations. All samples were analyzed by an accredited laboratory for total selenium (North/South 2008a,b).

## **2.1 Measured Fish Concentrations used to Characterize Impacts**

As people are more likely to consume larger fish than small minnows and that larger fish may contain higher selenium concentrations as a result of greater uptake, this assessment does not consider the selenium concentrations measured in longnose dace. Due to the limited number of available walleye, the current assessment is based solely on the measured selenium levels in white sucker from the NSR. For the reasons stated, use of white sucker as a surrogate fish species is considered a reasonable assumption when attempting to characterize the potential selenium-related health risks posed to people eating fish from the NSR.

Focus was given to the North/South (2008a) report (presenting data collected in Spring 2007), wherein selenium concentrations were measured in the muscle of fish. A subsequent study completed by North/South (2008b) only measured whole-body selenium concentrations. As people are most likely to eat fish muscle tissue, only these data were used in the current assessment.

Table 1 presents the measured muscle concentrations of selenium as reported by North/South (2008a) for large fish (white suckers) collected in the vicinity of the Scotford Complex. These values, which represent Total Selenium in fresh weight (i.e., wet weight or ww), were used in the characterization of potential health risks

**Table 1 Measured Total Selenium Concentrations in the Muscle of Fish Collected in the Vicinity of the Scotford Complex in the North Saskatchewan River (North/South 2008a)**

Area	Fish ID#	Muscle Selenium Concentration (µg/g ww)
Upstream	1	0.18
	2	0.79
	3	0.72
	4	0.72
	5	0.91
	6	0.45
	7	0.49
	8	0.75
Downstream	1	0.79
	2	0.54
	3	0.41
	4	0.36
	5	0.72
	6	0.68
	7	0.48
	8	0.38
Average		0.59
95UCLM		0.67
*The 95UCLM represents the 95 <sup>th</sup> percentile of the upper confidence limit on the mean. This value was calculated using U.S. EPA ProUCL software.		

## 2.2 Comparison to Selenium Concentrations in Fish from Other Parts of Alberta

As part of an ongoing monitoring program in the upper McLeod and Smoky River systems, Alberta Environment initiated a study to investigate and document selenium concentrations in Alberta fish. Table 2 shows tissue concentrations of selenium in fish collected from background or reference sites that are not thought to be affected by increased selenium inputs due to human activities.

**Table 2 Measured Concentrations of Selenium in Fish Muscle from Various Reference Sites in Northern Alberta (ASDR and AENV 2006)**

Reference Location	Fish Species	n°	Selenium (µg/g ww)		
			Average	Min	Max
<i>1999</i>					
Fairfax Lake	Rainbow Trout	3	0.14	0.13	0.15
Wampus Creek	Rainbow Trout	16	0.70	0.33	1.11
Whitehorse Creek	Rainbow Trout	10	1.05	0.86	1.24
<i>2000</i>					
Cold Creek	Brook Trout	14	0.49	0.11	0.72
Deerlick Creek	Rainbow Trout	17	0.41	0.22	0.91
Fairfax Lake	Brook Trout	8	0.19	0.05	0.33
Fairfax Lake	Rainbow Trout	12	0.15	0.05	0.32
Muskeg River	Brook Trout	1	0.91	0.91	0.91
Muskeg River	Bull Trout	12	0.70	0.56	0.82
Muskeg River	Rainbow Trout	12	0.87	0.86	1.09
Whitehorse Creek	Rainbow Trout	4	0.65	0.49	0.90
	<i>Total</i>	<i>109</i>	<i>0.57</i>	<i>0.05</i>	<i>1.24</i>

Selenium concentrations in muscle of fish collected from reference locations in Alberta ranged from 0.05 to 1.24 µg/g ww, averaging between 0.14 and 1.05 µg/g ww. Selenium concentrations in muscle of fish from the NSR ranged from 0.18 to 0.91 µg/g ww, with an overall average of 0.59 µg/g ww. The above data indicate that the selenium concentrations in fish collected from the NSR fall within the range of those collected from reference lakes and rivers in Alberta.

### 3.0 Assessment

#### 3.1 Exposure Assessment

Reliance was placed on the data for white suckers from North South (2008a) to predict potential human exposure to selenium via local fish consumption from the NSR. Specifically, the 95UCLM calculated on the North/South (2008a) white sucker muscle tissue data was used in the assessment.

Over a long-term exposure period, it is feasible that people would typically be exposed to selenium concentrations close to the average of the measured data. However, 95UCLM values were employed in an attempt to describe potential “high-end” exposures. As noted, fish muscle is likely to be the portion of the fish most commonly consumed by people and, as such, is considered more relevant when attempting to characterize potential risks to people eating those fish.

Health Canada’s (2007) recently recommended fish consumption rates were used in this assessment. The Bureau of Chemicals Assessment within Health Canada has adopted a fish consumption rate of 40 g/day to represent an adult “high-fish consumer” for the purposes of their hazard assessments (Health Canada 2007). Additional information regarding fish intake by children and toddlers was also provided by Health Canada

(2007). Table 3 presents a summary of the fish consumption rates and the body weights used to predict human exposure to selenium in this assessment.

**Table 3 Fish consumption rates and body weights used to characterize health risks**

Life stage	Fish Consumption Rate (g/day ww)	Body weight (kg)	Reference
Adult	40	70.7	Health Canada 2007
School-aged child	33	32.9	Health Canada 2007
Toddler	20	16.5	Health Canada 2007

The general formula used to calculate the estimated daily intake (EDI) of selenium via fish consumption is:

$$\text{Estimated Daily Intake} = \frac{\text{Concentration} \times \text{Consumption Rate}}{\text{Body Weight}}$$

Where:

- Estimated Daily Intake (EDI) = calculated daily intake of selenium from fish, in units of µg/kg /kg body weight per day
- Concentration = fish concentration, measured muscle as 95UCLM in units of µg/g wet weight
- Consumption Rate = assumed daily intake of fish, in units of g/day wet weight
- Body Weight (BW) = body weight in kg, specific to each life stage as per Health Canada (2004a)

The Canadian Council of Ministers of the Environment (CCME) used average concentrations of selenium in various media (i.e., food, soil, air and water), along with the typical rates of intake of those media, to calculate “background” estimated daily intakes for selenium. These background EDIs are intended to represent the average level of selenium exposure that a Canadian may receive on a continual basis. CCME (2007) determined background EDIs for adults, school-aged children and toddlers to be 135.7, 112.9 and 69.3 µg/day, respectively. When adjusting for body weight, this equates to 1.9, 3.4 and 4.2 µg/kg bw/day for adults, children and toddlers. The unadjusted EDIs are similar to the mean selenium intake of 114 µg/day reported by California’s Office of Environmental Health Hazard Assessment (OEHHA 2008).

In the current assessment, the background EDIs reported by CCME were added to the estimated daily intakes associated with eating NSR fish in order to characterize total potential exposure to selenium.

### 3.2 Exposure Limit

Selenium is a trace mineral that is essential to good health. Selenium is incorporated into proteins to make selenoproteins. The antioxidant properties of selenoproteins help prevent cellular damage from free radicals (NIH 2004). Excessive intake of selenium can result in a condition called selenosis. Symptoms of selenosis may include gastrointestinal upsets, hair loss, white blotchy nails, fatigue, irritability, and mild nerve damage. Selenium toxicity in North America is rare, with the only reported cases having been associated with industrial accidents and an error in manufacturing that led to exceedingly high levels of selenium in a market supplement (Hatchcock 1997; Goldhaber 2003).

The United States Environmental Protection Agency (U.S. EPA 1991) and the U.S. Agency for Toxic Substances and Disease Registry (ATSDR 2003) used the same epidemiological study to derive an exposure limit of 5 µg/kg bw/day for selenium. In the Yang et al. (1989) study, a No Observed Adverse Effect Level (NOAEL) of 15 µg/kg bw/day was identified for the incidence of clinical selenosis from a population in China. Both the U.S. EPA and the ATSDR applied an uncertainty factor of 3 to account for intraspecies differences, given the weight of evidence available (U.S. EPA 1991; ATSDR 2003).

In its guidance document on human health screening level risk assessment, Health Canada does not provide a toxicological reference value for selenium (Health Canada 2004b). Health Canada does, however, provide dietary reference intakes for selenium. According to Health Canada, selenium's recommended dietary allowance (RDA) for children and adults are 1.5 µg/kg bw/day and 0.8 µg/kg bw/day, respectively. Health Canada defines an RDA as the "average daily dietary intake level that is sufficient to meet the nutritional requirements" of the vast majority of a population. In other words, the RDA is the goal for usual intake by an individual (Health Canada 2006). Health Canada also offers tolerable upper intake levels for children and adults of 7.5 µg/kg bw/day and 5.7 µg/kg bw/day, respectively. An upper intake level (or UL) is "the highest average daily nutrient intake level likely to pose no risk of adverse health effects to almost all individuals in a given life-stage and gender group" (Health Canada 2006). Similarly, the upper limits of intake calculated by the U.S. National Academy of Science (NAS 2000) correspond to a daily intake of about 5.5 µg/kg bw/day<sup>1</sup>.

In their review of selenium's potential toxicity, Lawrence and Chapman (2007) point out that no clinical signs of selenosis have been reported at 700 µg/day (or 10 µg/kg bw-day for an adult), suggesting that the reference dose of 5 µg/kg bw/day may be overly protective. However, as neither the US EPA or ATSDR have revised their exposure limits, and the lowest Health Canada UL is comparable to the US EPA and ATSDR values, the exposure limit of 5 µg/kg bw/day was used in the health impact assessment of selenium concentrations measured in fish from the NSR.

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<sup>1</sup> Tolerable upper limits from the NAS (2000) were converted into daily doses using standard body weights from Health Canada (2004).

Finally, ATSDR (2003) notes that children may be less susceptible to the toxic effects of selenium than adults. In fact, children appear to have the highest need for selenium of any age group. Despite this, the health impact assessment considered the potential selenium risks to all applicable age groups.

### 3.3 Results and Discussion

Hazard Quotients (HQs) were calculated by dividing the estimated selenium exposure from fish consumption by the selected exposure limit (i.e. the reference dose of 5 µg/kg/day):

$$\text{Hazard Quotient (HQ)} = \frac{\text{Estimated Daily Intake } (\mu\text{g/kg bw/day})}{\text{Chronic Oral Exposure Limit } (\mu\text{g/kg bw/day})}$$

Table 4 presents the calculated estimated daily intakes and associated hazard quotients for the fish samples.

Interpretation of the hazard quotients proceeded as follows:

- $HQ \leq 1$  Signifies that the estimated exposure is less than or equal to the exposure limit (i.e., the assumed safe level of exposure). This indicates that negligible health risks are predicted.
- $HQ > 1$  Signifies that the exposure estimate exceeds the exposure limit. This suggests an elevated level of risk, the significance of which must be balanced against the degree of conservatism incorporated in the assessment (i.e., the margin of safety may be reduced but is not removed entirely).

**Table 4 Calculated daily intakes and hazard quotients of selenium associated with eating NSR fish harvested in the vicinity of the Scotford Complex**

	Adult	Child	Toddler
Estimated Daily Intake (µg/kg bw/day):			
Background	1.9	3.4	4.2
NSR Fish consumption	0.4	0.7	0.8
Total	2.3	4.1	5.0
Exposure Limit (µg/kg bw/day)	5.0	5.0	5.0
Hazard Quotient (unitless)	0.5	0.8	1.0

As shown, the estimated daily intakes related to the measured selenium concentrations in fish are below levels considered safe for human health in all cases. Total estimates of exposure, wherein the “fish-only” and background EDIs are summed, were either less than or equal to the regulatory-endorsed exposure limit. This suggests that human health risks associated with selenium exposure for the area’s “high-fish consumers” should be considered negligible.

The summed EDIs are below Health Canada's tolerable upper intake levels for adults and children and the NOAEL of 15 µg/kg bw/day established in the original Yang et al. (1989) study.

At present, there is a fish consumption advisory on sportfish caught from the NSR (Government of Alberta 2008). While this advisory is related to methyl mercury concentrations and not selenium, it is relevant to this assessment as it means that people probably eat much less locally caught fish than what was assumed for the characterization of potential health risks. The advisory states that women of child-bearing age and children under the age of 15 should not eat fish from the NSR at all, while adult males should limit their intake to one meal per week (Government of Alberta 2008). Health Canada (2007) states that an average serving of fish is approximately 150 grams for an adult. Therefore, a single serving of fish per week is equivalent to 21.4 grams per day. This consumption rate equates to a hazard quotient of 0.04 for adults, which is considerably less than the one presented in Table 4.

In addition, California's OEHHA (2008) has set a fish contaminant goal (FCG) for selenium of 7.4 µg/g. This FCG is based on a fish consumption rate of 32 grams per day and the same exposure limit used in the current assessment (i.e., 5 µg/kg bw/day). It is worth noting that all of the selenium concentrations measured in white suckers collected from the NSR by North/South (2008a) are below OEHHA's FCG. OEHHA bases its FCGs solely on public health considerations relating to exposure to individual contaminants, without regard to the "counterbalancing benefits of fish consumption or alternative risks of other protein sources that may be consumed in place of fish" (OEHHA 2008).

Health Canada (2007) notes that fish is a high-quality source of dietary protein, and also contains fatty-acids and vitamin D. Regular fish consumption has been associated with the prevention of various diseases and conditions (Health Canada 2007; Ginsberg and Toal 2009). Specifically, selenium intake has been linked to numerous health benefits, including the prevention of cardiovascular diseases, inflammatory conditions such as arthritis, possible cancer suppression and the enhancement of cognitive development (OEHHA 2008; Lawrence and Chapman 2007). In fact, selenium may play a mitigating role in the toxicity of mercury, the element upon which the NSR's fish consumption advisory is based (Berry and Ralston 2009). Selenium sequesters mercury and reduces its biological availability (Raymond and Ralston 2004). As well, selenoproteins, through their antioxidant properties, help eliminate reactive oxygen species induced by mercury (Chen et al. 2006; Ralston et al. 2008). As such, it is important to weigh the potential benefits of selenium intake when assessing the potential risks posed to area residents who eat fish from the NSR.

### **3.4 Potential sources of uncertainty**

Certain factors may have contributed to an over- or understatement of the potential health risks in the analysis. Some of these factors include:

- The fish species (white suckers) that served as the basis for this assessment were used to reflect potential tissue concentrations to which people may be exposed. It is

possible that the selenium concentrations in fish are variable, depending on factors such as fish species and size (etc). Whether or not the tissue concentrations may have been understated, the estimated daily intake values related to eating locally-caught fish are considerably lower than the exposure limit employed in the current assessment. As such, the impact on the results of the health assessment are likely minimal.

- The estimated daily intakes and associated hazard quotients are based on the assumption that people in the area are high fish consumers (i.e. they rely upon locally caught fish as a part of their diet). Data from Alberta Health and Wellness (1997) suggest that people consume a relatively low amount of locally caught fish. Given the access to supermarkets and other food sources, people are likely to obtain food (including fish) from sources other than the North Saskatchewan River that may have variable selenium concentrations. In addition, there is currently a fish consumption advisory in place on the North Saskatchewan river, restricting the consumption of fish to adolescent and adult males, and women of non-child bearing age (Government of Alberta 2008). As such, the predicted daily intakes and associated hazard quotients may vary accordingly.
- An absorption efficiency of 100% was assumed in this assessment. It is not known with certainty that the bioavailability of selenium from fish tissue is actually 100%. Variability in the absorption of selenium in relation to the form of selenium and the matrix in which it is found has been observed. It is possible that the absorption of selenium from fish tissue following ingestion by humans is less than 100%. Lawrence and Chapman (2007) suggest that the bioavailability of selenium from fish tissue is somewhere between 50 and 70%.
- Selenium status and the dietary status of a person (given that selenium absorption depends to some extent on the intake of other nutrients) both influence the extent of absorption and excretion of selenium, which affect the potential dose of selenium to which a person might be exposed.
- The exposure limit used in this assessment (5 µg/kg bw-day) was based upon the incidence of selenosis in China. In addition, an uncertainty factor of 3 was applied to account for inter-individual variability. As discussed under “pharmacokinetics” (see Appendix A), nutritional status and dietary selenium sources can influence the kinetics and toxicity of selenium. Given potential differences in nutritional status and dietary selenium sources between the Chinese study population and the Fort Saskatchewan area population, it is possible that the exposure limit used in the current assessment of fish overstates the toxicity of selenium.
- The health advantages related to eating fish and the essentiality of selenium are well-documented. However, any benefits associated with eating fish from the NSR were not accounted for in the characterization of the potential health impacts.

## **4.0 Conclusion**

Based on the data from the North/South (2008a) study, fish caught and eaten from the North Saskatchewan River are not anticipated to result in or be associated with selenium-related health impacts to the area residents. The estimated daily intakes of selenium due to the consumption of fish are below levels at which negative health effects might occur. Further, selenium concentrations in fish collected from the North Saskatchewan River appear to be similar to those collected in other parts of Alberta. For the reasons stated, the concentrations of selenium measured in fish collected in the vicinity of the Scotford complex can be considered safe for human consumption.

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**APPENDIX A**  
**Characterization of Selenium**

## **Appendix A: Characterization of Selenium**

This section is intended to provide background information in support of the main text. This information provides the reader with an understanding of selenium as it relates to human health.

### **1.0 Importance of Selenium**

The physiological functions of selenium as a nutrient in humans and animals include defense against oxidative stress (involving the action of glutathione), regulation of thyroid hormone activity, regulation of the reduction-oxidation status of vitamin C and other molecules (NAS 2000). Selenium deficiency can result in potentially severe effects and diseases as a result of nutritional, chemical or infectious agents (NAS 2000). For example, Keshan disease, a type of cardiomyopathy that occurs only in selenium-deficient children, can arise as a result of infection or exposures to chemicals. Keshan disease has been observed to occur in selenium-deficient populations within China (NAS 2000). Kashin-Beck disease, a disorder involving cartilage, has been observed in parts of Asia with low selenium intake levels (NAS 2000).

### **2.0 Potential for Exposure**

People may be exposed to selenium via drinking water, food, soils and air. The primary route of exposure is via food consumption (IPCS 1986; ATSDR 2003).

Natural food sources high in selenium include cereals, nuts, legumes, animal products and seafood (ODS 2004).

The two forms of selenium that are soluble in water are the alkali selenites (+4) and selenates (+6). These may be converted to organo-selenium compounds such as selenomethionine, selenocysteine, dimethyl selenide and dimethyl diselenide when taken up by plants. Aquatic organisms can convert selenium to both inert and soluble forms (ATSDR 2003). Both selenites and selenates were detected in surface water from the North Saskatchewan River by Stantec (2008), while all fish data from North/South (2008a,b) were presented as total selenium.

### **3.0 Pharmacokinetics**

#### **3.1 Absorption**

The most common forms of selenium in the human diet are highly bioavailable and are well absorbed (NAS 2000). Selenomethionine (from plants) and inorganic selenium compounds (from meat, fish and seafood) are sources of human exposure via food consumption (NAS 2000; ATSDR 2003). The primary site of

selenium absorption is the small intestine, with limited absorption occurring in the stomach (IPCS 1986).

A sizable fraction of selenate is excreted in the urine before it is absorbed into tissues (NAS 2000). Selenite absorption has been observed to be more variable and is better retained by the body than selenate (NAS 2000). Absorption of these two inorganic forms have been reported to range from 50 to 100% (NAS 2000).

Some variability in absorption from feed sources has been observed in a study in poultry (Gabrielsen and Opstvedt 1980). Selenium in mackerel feed has been observed to be higher than in capelin feed (6.2 vs. 1.4 mg/kg), suggesting that fish type may affect selenium content (Gabrielsen and Opstvedt 1980). The bioavailability of selenium from fish has been observed to range from 20 to 48% in studies where poultry were fed selenium containing diets and glutathione status was subsequently evaluated (Gabrielsen and Opstvedt 1980; Cantor and Tarino 1982). The availability of selenium from fish was observed to be higher than from soy (17.5%) or corn meal (25%) but less than selenium in the form of selenomethionine (78%) (Gabrielsen and Opstvedt 1980). While similar data from humans were not readily available, it is possible that some differences in the relative bioavailability of selenium from fish occur.

In addition, nutritional status has been reported to affect absorption. Selenium-deficient individuals are more likely to demonstrate a higher degree of selenium absorption (ATSDR 2003). Dietary selenium requirements are related to oxidant activity and other nutrients such as zinc, copper, manganese, iron and vitamin (Klaassen 1996). The presence of sulfhydryl-containing compounds in the gut has been observed to also affect the degree of absorption of selenium compounds (ATSDR 2003).

Overall, there appear to be differences in the extent of selenium absorption depending on whether selenium is administered independent of a food matrix, the type of food matrix (fish, plants etc.), and on a person's nutritional status.

### **3.2 Distribution**

Following absorption, selenium is widely distributed in the body. Several forms of selenium are present in blood and in metabolizing tissues (NAS 2000; ATSDR 2003).

Selenium distribution has been observed to be fairly independent of the form and route of administration given that the kidney and liver tend to be the tissues with the highest selenium concentrations (IPCS 1986). Selenium is also present in blood, brain, myocardial tissue, muscle, hair, and testes (Klaassen 1996). Organic selenomethionine has been observed in animal studies to accumulate to a greater extent than selenite or selenide (ATSDR 2003).

Selenium is distributed into two 'pools' within the body: selenium in the form of selenomethionine and in glutathione peroxidase enzymes (NAS 2000). Inorganic

selenium compounds tend to be distributed as glutathione peroxidases in the liver and in extracellular form in blood plasma, or as selenoproteins (NAS 2000).

In general, animal studies have observed a correlation between blood selenium levels and intake (IPCS 1986). Selenomethionine (from plants, primarily) is not regulated by a homeostatic mechanism and blood selenium levels are generally the highest following selenomethionine intake (rather than other forms of selenium). Selenomethionine may incorporate into proteins during synthesis in place of methionine, likely leading to an increase in blood selenium concentrations (NAS 2000).

### **3.3 Metabolism**

Ingested selenite is metabolized to selenide (NAS 2000) by glutathione-dependent reduction processes, primarily in red blood cells (ATSDR 2003). Selenate has been noted to be converted to selenide (NAS 2000); however, it has also been observed to be directly taken up by the liver and excreted (ATSDR 2003). Selenide is bound to albumin in plasma, and is transported to the liver where it may be further metabolized to selenophosphates or selenoproteins, or to excretory metabolites (NAS 2000). These selenoproteins are biologically active and have various physiologic functions (NAS 2000; ATSDR 2003). The primary mechanism of biotransformation of selenide appears to be methylation (Klaassen 1996). Dimethyl selenium is an intermediate in the formation of the urinary metabolite (trimethyl selenium). When selenium intake exceeds the rate of methylation, excess dimethyl selenium may be exhaled via the lungs (causing the characteristic garlic breath associated with acute selenium toxicity) (Klaassen 1996).

Selenomethionine is metabolized to selenide and incorporated into selenoproteins by metabolism to methane selenol and selenide, or to selenocysteine (ATSDR 2003).

### **3.4 Excretion**

The excretion of inorganic selenium has been observed to have two phases. The first phase is rapid, with 15 to 40% of the absorbed dose being excreted in the urine within a few days (Klaassen 1996). The remaining dose is excreted over a longer period of time (103 days for inorganic selenite and 234 days for organic selenomethionine) (Klaassen 1996). Fecal excretion has been observed to less than 10% (IPCS 1986). Some excretion may occur via exhalation, sweat, or in hair and nails, depending on the dose ingested (ATSDR 2003). The proportion excreted by each route has been reported to vary with dose ingested.

Nutritional status and dietary selenium intake both influence the route and rate of excretion of selenium from the body (ATSDR 2003).

## 4.0 Toxicity

The relative toxic potential of the inorganic and organic forms of selenium have been found to be similar with respect to clinical symptoms, but differ in the onset of symptoms.

Although inorganic selenium is not distributed as widely as selenomethionine and its blood concentrations are lower as a result of intake, exposure to inorganic selenium can result in adverse effects at lower concentrations (NAS 2000).

Inorganic selenium can cause toxicity at tissue levels of selenium much lower than seen with similar intakes of dietary selenium as selenomethionine. Given that selenomethionine is taken up into blood plasma, there is a delay in the onset of adverse effects as a consequence of protein binding. However, when people are chronically exposed, the effects and severity of selenium toxicity are similar for organic and inorganic compounds (NAS 2000).

Selenium status has been observed to affect selenium toxicity (IPCS 1986), potentially due to the increased availability of selenium in deficient individuals (ATSDR 2003).

### 4.1 Acute Toxicity

Characteristic signs of acute selenium toxicity following high doses include garlic breath odour, vomiting, muscle spasms, difficulties breathing, heart, kidney and liver tissue damage (IPCS 1986). Lethal doses at which 50 percent of the study population die (i.e., LD<sub>50</sub>) in oral rodent studies with sodium selenite have been observed to range from 2.25 mg/kg-bw (rabbit) to 13.2 mg/kg-body weight (rat) (IPCS 1986). The acute toxicity of sodium selenite, sodium selenate, selenocystine and selenomethionine have been observed to be relatively similar (IPCS 1986).

Accidental ingestion of large acute doses of selenium (> 25 mg or 25,000 µg per day) have been observed to result in garlic breath, gastrointestinal distress (dyspepsia, diarrhea, anorexia), neurological symptoms, liver damage, cardiac arrhythmia, changes in hair and nails and even death (Fan and Kizer 1990).

### 4.2 Chronic Toxicity

In animals, growth reduction is the most characteristic sign of chronic oral selenium toxicity (IPCS 1986). At doses above 8 mg/kg-body weight per day, hepatitis, renal and myocardial damage have been observed in rodents (IPCS 1986).

In humans, skin, hair and nail abnormalities are indicators of chronic over-exposure to selenium (ATSDR 2003). Symptoms of chronic selenium toxicity (known as “selenosis”) include hair and nail brittleness and loss, gastrointestinal problems, skin rashes, garlic breath, fatigue, irritability, nervous system effects (IPCS 1986; NAS 2000, ATSDR 2003). In addition, nervous system effects and

excess dental caries have been reported (Fan and Exon 1990). The mechanism(s) of these effects are not clear, but it is suspected that it may involve the substitution of selenium for sulphur in various synthetic processes (ATSDR 2003). Oxidative stress is also a suspected mechanism of selenium toxicity. Excess selenium has been observed to promote the formation of reactive superoxides, to interfere with the redox-regulating activities of various proteins and functional groups (ATSDR 2003). Selenium status (deficiency or excess) has also been observed to impact thyroid hormones, and indirectly, the neuroendocrine system (ATSDR 2003).

Incidences of chronic selenosis have not been observed in the United States (outside of occupational or accidental exposures), including areas where soil selenium levels are naturally high (ATSDR 2003). This is suspected to be the result of the selenium exposures in the North American diet being adequate and not excessive (Fan and Kizer 1990).

#### **4.3 Reproductive and Developmental Toxicity**

No studies regarding reproductive effects in humans are available. However, some animal studies have observed impaired fertility and reduced conception rates (ATSDR 2003). Selenium has not been reported to induce developmental effects in humans. Mammalian studies suggest that the threshold for developmental effects is relatively high, given that abnormalities were only observed at dose levels associated with overt maternal toxicity (ATSDR 2003). In contrast, selenium is a known reproductive toxicant in birds (IPCS 1986).

#### **4.4 Carcinogenicity**

The International Agency for Research on Cancer has classified selenium as Group 3: not classifiable as to its carcinogenicity to humans. Included in this classification are sodium selenate, sodium selenite and organic selenium compounds (ATSDR 2003).

Selenium sulfide is the only selenium compound that has been observed to be associated with tumourigenicity in animals. Selenium sulfide is not found in foods (ATSDR 2003).

### **5.0 Recommended Intakes**

In animal studies, selenium intakes of 5 mg/kg-bw per day or higher have been observed to be associated with chronic selenosis in livestock and rodents (IPCS 1986). Dietary selenium intakes required to prevent deficiency in most animals species range from 0.02 to about 0.05 mg/kg-bw-day (IPCS 1986). Health Canada (2006) bases its Recommended Dietary Intakes (RDI) on those of the U.S. National Academy of Science. The Health Canada RDIs for adults and toddlers are 0.055 and 0.020 mg/day (about 0.0008 mg/kg-bw/day and 0.0012 mg/kg-bw/day).

Based upon a review of human epidemiological data, the U.S. National Academy of Science determined the No Observed Adverse Effect Level (NOAEL) for selenium to be 0.8 mg/day and the Lowest Observed Adverse Effect Level (LOAEL) to be 0.9 mg/day in adults. Selenium intakes greater than 1 mg/day have been observed to be associated with chronic selenosis (Koller and Exon 1985). The U.S. National Academy of Science has determined that the Tolerable Upper Intake Level (UL) for selenium intake in adults should be set at 0.4 mg (approximately 0.0057 mg/kg-bw) based on the potential for selenosis (NAS 2000). In toddlers the UL is estimated to be about 0.09 mg/day by the NAS (2000) (equivalent to approximately 0.0055 mg/kg-bw per day).

A Therapeutic Index (TI) is a tool used by toxicologists to evaluate the toxicity of a substance in relation to its desired therapeutic effects. A TI represents the ratio of the dose required to produce a toxic effect to the dose required to induce the desired effect (Klaassen 1996). In the case of selenium, the TI may be determined by comparing the dose above which adverse effects may occur in humans (i.e. the NAS NOAEL of 0.8 mg/day) to the dose that is required to prevent symptoms of deficiency (i.e. the Health Canada RDIs). Assuming an average body weight of 70.7 kg for an adult (from Health Canada 2004), the TI for selenium is approximately 15. Although there is no clear metric, a therapeutic index of 10 or more indicates a relatively safe substance (Klaassen 1996).

## 6.0 References

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