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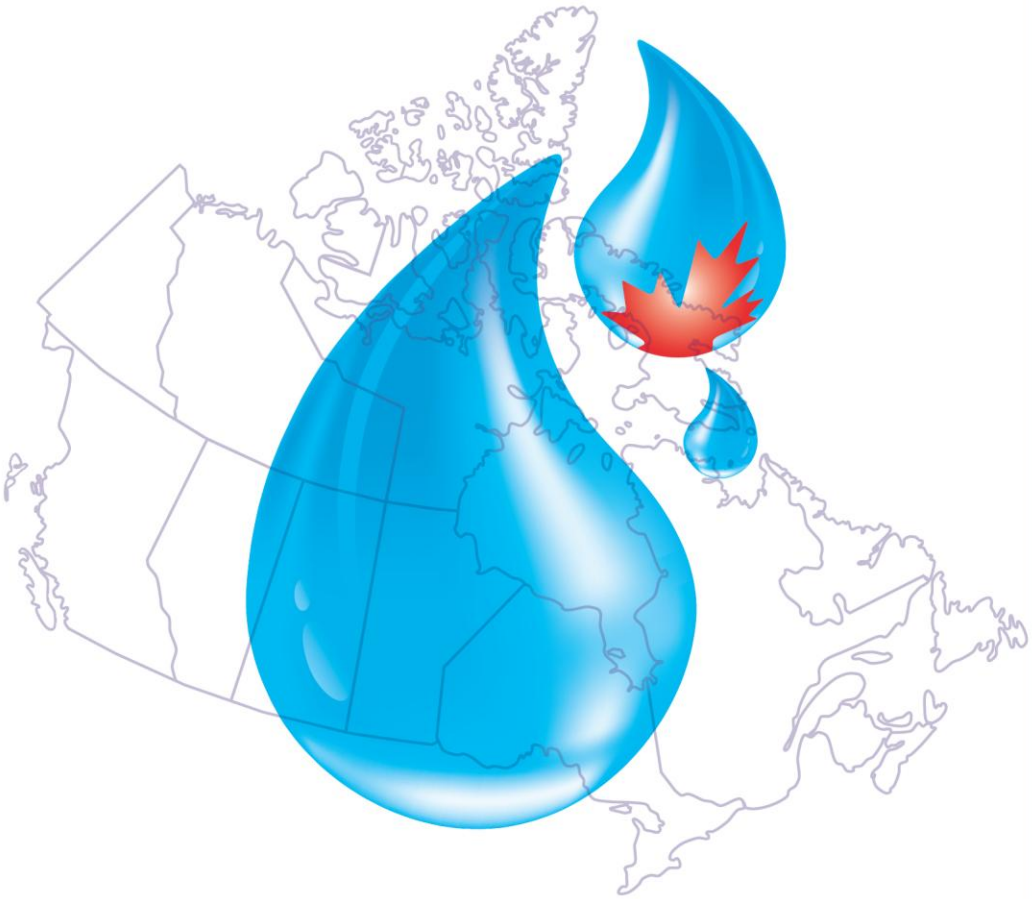
Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Selenium



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Guideline Technical Document

Selenium

Prepared by the
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Drinking Water
of the
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Health and the Environment

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Other Guideline Technical Documents for the Guidelines for Canadian Drinking Water Quality can be found on the following web page: www.healthcanada.gc.ca/waterquality

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March, 2014

Selenium

Part I. Overview and Application

1.0 Guideline

The maximum acceptable concentration (MAC) for total selenium in drinking water is 0.05 mg/L (50 µg/L).

2.0 Executive summary

Selenium is a naturally occurring element which is ubiquitous in the environment. It is generally present in elemental form or in the form of selenide (Se^{2-}), selenate (SeO_4^{2-}), or selenite (SeO_3^{2-}). It is widely distributed in the Earth's crust and is found in trace quantities in most plant and animal tissues. Selenium is not directly mined, but rather is a by-product of the production of other metals. Selenium is used in the manufacture of organic chemicals, reducing agents, glass, paint, ceramic, electronic components, gun bluing agents, nutritional supplements, fertilizers, metallurgical applications and plumbing (as a replacement for lead).

This guideline technical document reviews and assesses all identified health risks associated with selenium in drinking water. It assesses new studies and approaches and takes into consideration the availability of appropriate treatment technology. Based on this review, the guideline for selenium in drinking water is a maximum acceptable concentration of 0.05 mg/L.

2.1 Health effects

Selenium is an essential trace element in the human diet. It is a component of several proteins and enzymes in the body that are known to play important roles, including regulation of thyroid hormones and antioxidant defences. A deficiency in selenium may lead to chronic diseases such as Keshan disease (characterized by cardiomyopathy) and Kashin-Beck disease (characterized by rheumatism) and may also be associated with a form of cretinism related to hypothyroidism. Selenium has minimum daily dose requirements set by international organizations. Health Canada adopted the recommended daily intake for selenium established by the Institute of Medicine (2000) which varies between 15 and 55 µg per day as a minimum selenium intake, depending on the age group. Selenium deficiency is not expected to be a concern in Canada.

Selenium has been classified by the International Agency for Research on Cancer in Group 3: not classifiable as to its carcinogenicity to humans. The vast majority of the literature does not demonstrate an increase in cancer incidence following selenium exposure; a protective effect has even been suggested. A non-cancer approach was used in this assessment, and the MAC for selenium in drinking water is based on chronic selenosis symptoms in humans. Selenosis symptoms resulting from chronic exposure to high levels of selenium are characterized by hair loss, nail anomalies or loss, skin anomalies, garlic odour of the breath, tooth decay and, more severely, disturbances of the nervous system. Links have also been found between selenium exposure and other diseases such as diabetes and glaucoma, but results need to be confirmed before conclusions can be drawn.

2.2 Exposure

Canadians can be exposed to selenium through its presence in food, air, soil, drinking water, as well as through the use of specific consumer products or in occupational settings, with food being the main source of exposure. Selenium levels are generally low in Canadian drinking water supplies. Inorganic forms of selenium that are normally found in drinking are not volatile and very little quantitative information is available on the absorption of selenium compounds through the lungs or skin. Selenium deficiency is not likely to be a concern in Canada.

2.3 Analysis and treatment

There are several analytical methods available for the analysis of total selenium in drinking water at levels well below the MAC. The speciation of selenium in the raw water plays a critical role in the effectiveness of treatment methods used for the removal of selenium. The removal of excess selenium from drinking water has not been studied on a full-scale treatment plant basis, and limited data exist on laboratory and pilot plant tests. Nevertheless, there are several technologies that can remove selenium from drinking water. There are drinking water treatment devices certified for the removal of selenium. The treatment processes that are capable and able to be certified for selenium removal at the residential scale include adsorption, reverse osmosis and distillation.

3.0 Application of the guideline

Note: Specific guidance related to the implementation of drinking water guidelines should be obtained from the appropriate drinking water authority in the affected jurisdiction.

The maximum acceptable concentration for selenium is established based on chronic symptoms of selenium toxicity in the general population. Short-term exceedances slightly above the guideline value are unlikely to have an effect on health.

3.1 Monitoring

Frequent monitoring of naturally-occurring selenium levels is generally not required, as these levels are not expected to change rapidly. Since the potential release of selenium is likely to be into source waters through coal ash pond effluent and the ash and dusts that settle on water, monitoring of source water near coal-fired power plants and in areas where mining and refining of copper and other metals occurs is recommended. In the event that monitoring data show elevated levels of naturally-occurring selenium, it is suggested that a plan be developed and implemented to address these situations.

Part II. Science and Technical Considerations

4.0 Identity, use and sources in the environment

Selenium (CAS Registry No. 7782-49-2) is a metalloid with both metallic and non-metallic properties. It is present in the environment in both inorganic and organic forms. Inorganic forms of selenium include selenide (oxidation state −2, H_2Se), elemental selenium (oxidation state 0) and the species selenite (oxidation state +4, SeO_3^{2-}, $HSeO_3^-$) or selenate (oxidation state +6, SeO_4^{2-}, $HSeO_4^-$). Organic forms of selenium include selenomethionine and selenocysteine, which can be found in plants (ATSDR, 2003; Johnson et al., 2010; Dennert et al., 2011; Ferguson et al., 2012).

Selenium is found naturally throughout the environment. The elemental form of selenium in the environment is rare; selenium is mostly found in combination with other elements (ATSDR, 2003). In soil, the most common forms of selenium are selenate and selenite. Selenide, selenium sulphide and elemental selenium are essentially insoluble and tend to be immobile in soils (U.S. EPA, 1990a; ATSDR, 2003). The elemental form of selenium has appreciable volatility and hence will enter the atmospheric environmental compartment, as will selenium dioxide (e.g., in emissions from smelting operations and coal burning) and volatile organoselenium compounds produced by plants (IARC, 1975). Selenium compounds may be methylated by soil microorganisms, such as bacteria and fungi, and by plants and animals. The methylated species volatilize to the atmosphere (Shamberger, 1981). During volcanic activity, selenium present in the lava volatilizes, explaining the low concentration found in magmatic rocks (Fordyce et al., 2000). Rock erosion results in selenium entering oceans and inland waters (IARC, 1975); thus, selenate and selenite can be found in fresh water and seawater (U.S. EPA, 1990a; CCME, 2009). Selenate and selenite are soluble and mobile in soil. The form of selenium in the soil and its bioavailability depend on pH, texture, mineralogy, the presence of competing ions (PO_4^{3-} and SO_4^{2-}) and the organic matter content of the soil. An increase in pH, oxidizing conditions and a low organic matter content increase the formation of soluble and mobile species. An alkaline soil environment favours the formation of selenate (CCME, 2009; Johnson et al., 2010), which is thus more readily available than selenite for plant uptake and utilization (Fairweather-Tait et al., 2011). In acidic soil, selenite combines with ferric oxide and clays to form less soluble complexes.

Anthropogenic release is considered the main factor in selenium migration (Johnson et al., 2010). Coal ash from coal-fired power plants and mining and refining of copper and other metals are the main human-caused sources of selenium in water (Casey and Siwik, 2000; ATSDR, 2003). When coal is burned, selenium is released to the atmosphere. Selenium can enter water bodies through coal ash pond effluent and the ash and dusts that settle from the atmosphere on water (Fishbein, 1983).

Selenium compounds are used in the laboratory for the synthesis of organic chemicals and as reducing agents. They are used by the glass, paint, plastics and ceramic industries to produce tints and colours, and selenium is present at high concentrations in gun bluing agents, which are lubricants to polish metals (ATSDR, 2003). Selenium's semiconductor properties are utilized in electronics and photoelectric cells. Selenium is also used as a replacement for lead in brass alloy plumbing fittings, in nutritional supplements, as an agricultural fertilizer and in metallurgical applications (ATSDR, 2003; CCME, 2009).

Selenium is not directly mined, but rather is a by-product of the production of other metals (Johnson et al., 2010). Selenium production in Canada is divided among three provinces. In 2010, 18, 58 and 22 tonnes were mined in Quebec, Ontario and Manitoba, respectively

(Natural Resources Canada, 2010); in 2011, 19 and 16 tonnes were mined in Quebec and Ontario, respectively (Natural Resources Canada, 2011).

5.0 Exposure

Canadians can be exposed to selenium through its presence in air, food, consumer products, soil and drinking water. The main source of selenium exposure is through diet. Selenium is an essential element and has minimum daily dose requirements set by international organizations (Institute of Medicine, 2000; WHO and FAO, 2004; Otten et al., 2006).

Although some exposure data are available, they are not sufficient to modify the default proportion (20%) of the daily intake allocated to drinking water (allocation factor) in the calculation of the maximum acceptable concentration.

5.1 Drinking water

Selenium levels in drinking water are generally low, but can vary depending on geological formations (CCME, 2009). The selenium concentrations in drinking water were measured in various locations across Canada as part of the National Survey of Disinfection By-Products and Selected Emerging Contaminants in Canadian Drinking Water (Health Canada, 2012a). Source water, treatment facilities and various points in distribution systems were sampled and analysed for dissolved and total selenium (after acid digestion). All samples (n = 65) collected in 2009/2010 were below the detection limit of 2 µg/L. However, it should be noted that any selenium leached from plumbing materials would not have been captured in this survey.

Provincial and territorial data were obtained from members of the Federal-Provincial-Territorial Committee on Drinking Water in 2012, and show the levels of selenium found in drinking water systems across Canada.

In Newfoundland and Labrador, data were provided for source and tap water since 2002 (Newfoundland and Labrador Department of Environment and Conservation, 2012). In tap water, 8246 out of 8689 (95%) samples were below the detection limit of 1 µg/L; 416 (5%) samples had selenium concentrations between 1 and 5 µg/L; and 27 (0.3%) samples had selenium concentrations between 5 and 11 µg/L. Similar measurements were shown for source water.

In Nova Scotia, selenium was above the detection limit of 2 µg/L in only 19 out of 1055 samples (1.8%) of raw or treated drinking water sourced from surface water, groundwater or distribution system collected between 2000 and 2012 (Nova Scotia Department of the Environment, 2012). The average selenium concentration was 2.1 µg/L, and the maximum concentration was 12 µg/L. Five of the 19 samples were from surface water, and the selenium concentrations in these samples were in the range 1–2 µg/L.

In New Brunswick, the majority of raw surface water and groundwater samples were below the detection limit of 2 µg/L for selenium in measurements done between 1994 and 2012 in Crown lands and between 2008 and 2012 in municipal lands (New Brunswick Department of Health and Wellness, 2012). There is no drinking water treatment system in the province (municipal or Crown) designed specifically to treat for selenium. In the Crown and municipality water samples, 127 out of 5159 (2.5%) had selenium concentrations above 2 µg/L, with a mean concentration of 2.5 µg/L and a maximum concentration of 10.4 µg/L.

In Quebec, 3698 drinking water distribution installations measured 14 083 samples of water for selenium from 2005 to 2009. Three percent (424/14 083) of the measurements were above the detection limit (0.1 µg/L), and 0.05% (7/14 083) were above 10 µg/L, with the highest

value being 27 µg/L (Ministère du Développement durable, de l'Environnement et des Parcs du Québec, 2012). Of these, the majority were samples from groundwater supply without filtration.

In Ontario, 38 out of 3427 samples (1.1%) collected between 2007 and 2011 contained selenium at concentrations above 2 µg/L (Ontario Ministry of the Environment, 2012). Selenium was detected in all 37 samples of raw and treated groundwater collected in Walkerton, at concentrations ranging between 11 and 16 µg/L.

Selenium has been measured at levels of 0.011–0.043 µg/L in six locations of the west arm of Lake Erie (Adams and Johnson, 1977).

In First Nations of Manitoba, the selenium content of tap water was analysed in 8–23 households in nine communities from the six ecozones of the province (Chan et al., 2012). Selenium was present at concentrations below the detection limit of 0.2 µg/L in four ecozones, and the maximum concentration detected in all ecozones was 3.5 µg/L. Most of the water supply of the communities comes from surface water: four from lakes, three from rivers and two from groundwater.

In Saskatchewan, the vast majority of selenium concentrations measured in groundwater, surface water and treated drinking water samples collected between 2001 and 2011 were below the detection limit of about 1 µg/L (Saskatchewan Department of Environment and Resource Management, 2012). In general, Saskatchewan was found to have higher levels of selenium than other provinces and territories. Concentrations above 2 µg/L were detected in 7.2 % (217 out of 2997) of the samples measured in groundwater, surface water and treated drinking water and above 10 µg/L in 1.3% of the samples.

In west-central Saskatchewan and east-central Alberta, selenium was below the detection limit of 0.1 µg/L in six samples taken from the Battle River (Anderson, 1994).

In British Columbia, the Ministry of Environment reported that selenium was monitored in various rivers, and concentrations ranged from 2 to 9 µg/L. The concentration of selenium in water in a coal mining area was 2.5 µg/L (Nagpal and Howell, 2001).

In First Nations of British Columbia, the selenium content of tap water was analysed in 21 communities distributed among the eight ecozones of the province. Selenium was present at concentrations below the detection limit of 0.2 µg/L in three ecozones, and the maximum concentration detected in all ecozones was 1.4 µg/L. Source water supply varied between communities: 14 come from wells, 6 from creeks/streams, 2 from a river and 4 from lakes (Chan et al., 2011).

The Northwest Territories tested for selenium in raw or treated drinking water in 24 communities in 2009. Selenium was below the detection limit of 0.2–1 µg/L in 21 communities and detected in 3 communities at 0.2–0.9 µg/L (Government of the Northwest Territories, 2011).

5.1.1 Leaching from non-leaded brass components

Historically, leaded brasses used in potable water systems have been found to leach lead. Alternative non-leaded brass alloys have been developed—i.e., brass with no lead intentionally added and the lead replaced with other metals, such as bismuth, selenium and phosphorus. These metals improve the mechanical characteristics of the brass. However, there are limited data on the potential of non-leaded brass to leach metals. The Water Research Foundation has funded two projects on leaching of non-leaded brasses, which are currently in progress.

Brass is generally used in applications for distribution system and premise plumbing components (i.e., fittings), including brass components used with plastic piping. NSF International (NSF)/American National Standards Institute (ANSI) Standard 61 (NSF/ANSI, 2011a) is a health-based leaching standard which limits the leaching of selenium into drinking water to 0.005 mg/L. Under the National Plumbing Code of Canada, fittings must meet the

requirements of plumbing standards for plumbing supply fittings, components and plastic pipes (NRCC, 2010). The Canadian Standards Association (CSA) standard for plastic pipes and the harmonized American Society for Mechanical Engineers/CSA standard for plumbing supply fittings as well as plumbing fittings (CSA, 2011a,b) require that components used for drinking water applications comply with the requirements of NSF/ANSI Standard 61. Materials in contact with drinking water meeting NSF/ANSI Standard 61 would be expected to leach very low amounts of selenium into drinking water.

5.2 Food

Food is the main source of exposure to selenium. The major selenium species present in food are organic. Organic selenium is contained in the amino acid derivatives selenomethionine and selenocysteine, which are highly bioavailable (IPCS, 2006; Norton and Hoffmann, 2011). Although present in lower quantities, inorganic selenite and selenate can also be found in vegetables and mushrooms (Whanger, 2002; Thiry et al., 2012).

Concentrations of selenium in food items vary between countries and regions and depend on the food item and soil conditions. Concentrations can even vary within a single plant (Valdiglesias et al., 2009; Lemire et al., 2010). For example, the selenium content of Brazil nuts was found to range from 0.03 to 512 µg/g in the high-selenium area covered by the Tapajos River basin in Brazil. In Canada, selenium concentrations found in common food items vary; entrails and internal organs, beef meats, fish, eggs and Brazil nuts have a content generally between 30 and 310 µg/kg, vegetables generally between 1 and 100 µg/kg, and whole cow milk and cereals around 10–1350 µg/kg (Valdiglesias et al., 2009). Baked goods and bread are the main sources of selenium in food in Canada and contribute to 51% of the intake (Dabeka, 1994). The Canadian Total Diet Study (TDS) is a Health Canada initiative that measures the dietary intakes of different chemicals for different age–sex groups of the Canadian population (Health Canada, 2011). For adults, the average dietary intakes of selenium were estimated at 1.9 µg/kg body weight (bw) per day in 2005 (Toronto) and 2006 (Halifax) and 2.7 µg/kg bw per day in 2007 (Vancouver). This study attested that food is the main source of selenium intake and found that dietary exposure to selenium ranged from 113 to 220 µg/day in Canadian adults, based on four different diets in Winnipeg, Halifax and Toronto (see Table 1 in Section 5.8 below for a summary). These estimates are within the range of those provided in a report published in 1975, indicating that selenium exposure from food has not changed substantially since then (Thompson et al., 1975).

According to the data from the TDS, the dietary intakes of selenium were 4.5 µg/kg bw per day in 2005 (Toronto), 4.4 µg/kg bw per day in 2006 (Halifax) and 7.7 µg/kg bw per day in 2007 (Vancouver) for infants 0–6 months of age. Selenium concentrations in powdered infant formula ranged from 25.1 to 49 ng/g in Canada, based on TDS data from 2005 (Toronto), 2006 (Halifax) and 2007 (Vancouver) (Health Canada, 2011). In a study conducted in the Ottawa area, infant formulas (prepared with demineralized, deionized water) were found to contain selenium at concentrations of 3–21 µg/L (unsupplemented formula) and 16–35 µg/L (supplemented formula) (L'Abbé et al., 1996). Assuming an average consumption rate of infant formula of 0.75 L/day by infants 0–6 months of age that are exclusively formula fed (Health Canada, 1994), this provides 2.2–15.7 and 12.0–26.2 µg of selenium per day for the unsupplemented and supplemented formulas, respectively (Health Canada, 1994). Breast milk samples from women in eastern Ontario contained 13–25 µg of selenium per litre, providing infants with an estimated exposure of 11–20 µg/day (L'Abbé et al., 1996).

5.3 Air

The mean concentrations of selenium in particulate matter less than or equal to 10 µm in diameter in the air of 22 Canadian cities in 2009 were between 2 and 5 ng/m^3 (Environment Canada, 2012). Based on these low concentrations of selenium in ambient air, intake from air would be negligible compared with that from other media.

5.4 Consumer products

Selenium supplements in the form of natural health products are available from organic and inorganic sources at doses between 3.5 and 400 µg/day in Canada (Health Canada, 2007). Sources of selenium in nutritional supplements include selenium salts, such as selenium citrate, sodium selenate and sodium selenite, and selenium chelates from hydrolysed vegetable and animal protein, which are also known as selenium proteinates. The selenium monograph of Health Canada's Natural Health Products Directorate (Health Canada, 2007) suggests a safe product dose of up to 400 µg daily for selenite, selenate and organoselenium, based on the Institute of Medicine's recommendations (Otten et al., 2006).

Selenium sulphide is used in pharmaceuticals and cosmetics. For example, antidandruff shampoo containing selenium sulphide is classified as a natural health product in Canada. Absorption is unlikely from this cosmetic usage, as there is no substantial dermal penetration of this form of selenium through intact skin (IARC, 1975).

5.5 Soil

The presence of selenium in soil varies widely and is a reflection of the mineralogy of the parent material (Whanger, 1989). In Earth's crust, concentrations of selenium are relatively low in general (0.05–0.09 mg/kg), and the world mean concentration is 0.4 mg/kg (range of 0.01–2 mg/kg) (Fordyce et al., 2000; Johnson et al., 2010). In seleniferous areas, concentrations of 1200 mg/kg have been measured (Fordyce et al., 2000). Sedimentary rocks tend to have higher concentrations, but concentrations rarely exceed 0.1–0.3 mg/kg (Johnson et al., 2010). Also, very high concentrations of selenium have been observed in phosphate rocks (> 300 mg/kg) and coal and black shales (20 to > 600 mg/kg).

The content of selenium in the soil was analysed for five Canadian regions (Appalachian, Canadian Shield, St. Lawrence Lowlands, Interior Prairies and Cordilleran). For all regions combined, the selenium concentrations ranged from 0.02 to 3.7 µg/g of soil, and a mean concentration of 0.30 µg/g of soil was reported (CCME, 2009).

5.6 Blood levels in the Canadian population

Biomarkers of exposure have been used extensively in epidemiological studies on selenium (Mayne, 2003). Selenium levels in blood compartments (plasma, serum, erythrocytes) and urine are the most commonly used biomarkers and represent recent exposure (Rajpathak et al., 2005). In addition, selenium levels in blood are also good biomarkers of long-term exposure to dietary selenium (Longnecker et al., 1991). In contrast, selenium concentrations in nails and hair are measurements of long-term exposure (Rajpathak et al., 2005).

Statistics Canada, Health Canada and the Public Health Agency of Canada launched Cycle 1 of the cross-sectional Canadian Health Measures Survey to collect health data and biological specimens in approximately 5600 Canadians aged 6–79 years distributed among five age groups (6–11, 12–19, 20–39, 40–59 and 60–79 years) at 15 sites between 2007 and 2009. The geometric mean whole blood selenium concentration was 201 µg/L (95% confidence interval [CI] = 197–206 µg/L), and the geometric mean urinary selenium concentration was 49 µg/L (95% CI = 45–53 µg/L; n = 5492), for the total Canadian population aged 6–79 years

(Health Canada, 2010a). Whole blood selenium concentrations ranged from the 10th percentile of 169 µg/L to the 95th percentile of 253 µg/L. No data were provided for children under 6 years of age.

In Quebec, a cross-sectional survey collected data in 2001 on trace metals in men and women 18–65 years of age (n = ~500) residing in the Quebec city area (Leblanc et al., 2004). Levels of selenium in whole blood (geometric mean concentration 2.8 µmol/L, equivalent to 221 µg/L) and serum (geometric mean 1.7 µmol/L, equivalent to 134 µg/L) were reported.

5.7 Total daily intake

The estimated total daily intakes of selenium from drinking water, air, soil and food for the 0- to 6-month, 7-month to 4-year and 20+-year age groups in the Canadian population are shown in Table 1. Daily selenium intakes from dietary supplements and other consumer products were not estimated, as there are no available data on the proportion of the general population using these products. Individual variability of selenium intakes is possible for each source.

Table 1: Estimated daily intakes of selenium for various age groups in the Canadian general population

Age group	Daily intake of selenium from various sources (µg/kg bw per day)				
	Drinking water[a]	Air[b]	Soil[c]	Food[d]	Total
0–6 months non-breastfed infants	0.21	0.000 98	0.001 5	5.6	5.8
0–6 months breastfed infants	0	0.000 98	0.001 5	1.9	1.9
7 months to 4 years	0.12	0.001 3	0.001 1	5.6	5.7
20+ years	0.043	0.001 1	0.000 086	2.2	2.2

[a] **Drinking water:** Calculated using the provincial and territorial data reported in section 5.1, assuming an intake of 0 L/day in 0- to 6-month-old breastfed infants, 0.75 L/day in 0- to 6-month-old non-breastfed infants, 0.8 L/day in 7-month- to 4-year-old children and 1.5 L/day in adults and body weights of 7 kg, 7 kg, 13 kg and 70 kg, respectively (Health Canada, 1994). A representative estimate of 2 µg/L for selenium found in drinking water was used, considering that the vast majority of the samples were below the detection limit (1–2 µg/L).

[b] **Air:** Calculated from selenium measurements in the air of 22 Canadian cities, with a mean of 3.439 ng/m^3 (Environment Canada, 2012), and assuming an inhalation rate of 2 m^3/day in 0- to 6-month-old infants, 5 m^3/day in 7-month- to 4-year-old children and 20 m^3/day in adults (Health Canada, 1994).

[c] **Soil:** Calculated from the mean selenium concentration in soil of 0.3 µg/g (CCME, 2009), assuming an ingestion rate of 35 mg/day in 0- to 6-month-old infants, 50 mg/day in 7-month- to 4-year-old children and 20 mg/day in adults (Health Canada, 1994).

[d] **Food:** Dietary intakes represent average measurements from samples taken in Toronto, Halifax and Vancouver during the Canadian TDS (Health Canada, 2011): 5.6 µg/kg bw per day in 0- to 6-month-old non-breastfed infants, 5.6 µg/kg bw per day in 7-month- to 4-year-old children and 2.23 µg/kg bw per day in adults. Dietary intake for 0- to 6-month-old breastfed infants was calculated using an average selenium level of 17.7 µg/L in breast milk (L'Abbé et al., 1996).

The Institute of Medicine (2000) derived tolerable upper intake level (ULs) for selenium of 45 µg/day for infants aged 0–6 months, 60 µg/day for infants aged 7–12 months, 90 µg/day for children 1–3 years of age, 150 µg/day for children 4–8 years of age and 280 µg/day for children 9–13 years of age. The UL for infants aged 0−6 months was based on a human milk selenium concentration (*n* = 241 U.S. women from 17 states) of 60 µg/L that was without adverse effects in a study done by Shearer and Hadjimarkos (1975). The UL for adults of 400 µg/day was derived based on the studies of Yang and colleagues (Yang et al., 1989a,b; Yang and Zhou, 1994). The infant UL and the adult UL are similar on a body weight basis. Also, there is no evidence indicating increased sensitivity to selenium toxicity for any age group. Thus, the UL of 7 µg/kg bw/day was adjusted for older infants, children and adolescents on the basis of relative body weight.

6.0 Analytical methods

The United States Environmental Protection Agency (U.S. EPA) has three approved analytical methods (Method 200.5 Rev. 4.2, Method 200.8 Rev. 5.4 and Method 200.9 Rev. 2.2) for the analysis of dissolved and total selenium in drinking water (U.S. EPA, 2011). Total selenium is defined as the sum concentration of the dissolved ([selenite-Se(IV)] and [selenate-Se(VI)]) and the suspended fractions of a water sample. The following methods, developed by voluntary consensus standard organizations, are approved by the U.S. EPA and available for the analysis of selenium: SM 3113 B and SM 3114 B (APHA et al., 1992, 1995, 2005), online version SM 3113 B-04, 99 and SM 3114 B-09, 97 (U.S. EPA, 2011) and ASTM - D3859-98 A,B, D3859-03 A,B and D3859-08 A,B (ASTM, 1998, 2003, 2008).

Method 200.5 Rev. 4.2, which employs axially viewed inductively coupled plasma atomic emission spectrometry, has a method detection limit (MDL) of 1.3 µg/L. When this method is used, sample preparation procedures, such as preliminary recoverable digestion and preconcentration prior to analysis, are required. The preconcentration step prior to the analysis increases the analytical sensitivity (U.S. EPA, 2003). Possible interferences that may occur include: 1) spectral interferences, caused by background emission, stray light from the line emission of high-concentration elements or overlap of a spectral line from another element; 2) chemical interferences, such as molecular compound formation, ionization effects and solute vaporization effects; 3) physical interferences associated with the sample nebulization and transport processes; and 4) memory interferences, when analytes in a previous sample contribute to the signals measured in a new sample.

Both U.S. EPA methods 200.8 Rev. 5.4 and 200.9 Rev. 2.2 provide procedures for the determination of dissolved and total recoverable selenium. The methods applied use the same preservation and/or pretreatment steps, depending on the types of data required. The differences between these methods are in the equipment used for the measurement.

Method 200.8 Rev. 5.4, based on inductively coupled plasma mass spectrometry, has an MDL of 7.9 µg/L. The sample is atomized and ionized into radio-frequency plasma. The ions are extracted from the plasma by a vacuum interface and separated on the basis of their mass-to-charge ratio by a mass spectrometer. Separated ions are detected by an electron multiplier or Faraday detector (U.S. EPA, 1994). Interferences may be caused by: 1) equal mass isotopes of different elements present in the sample; and 2) ions consisting of more than one atom that have the same nominal mass-to-charge ratio as the isotope of interest. Physical interferences associated with the transport and conversion of the sample into the plasma and memory interferences, when isotopes of elements in previous samples contribute to the signals measured in a new sample, may also occur.

Method 200.9 Rev. 2.2, which uses stabilized temperature platform graphite furnace atomic absorption, has an MDL of 0.6 µg/L. The technique includes a series of three heating steps: 1) a drying step, 2) a charring step designed to reduce interferences caused by concomitant ions; and 3) a final step in which the temperature of the furnace is raised and selenium is atomized from the pyrolytic graphite surface into an atmosphere of high-purity argon. The light of a specific wavelength is passed through the atomic cloud, and the measurement is made of the attenuation of the intensity of the light (U.S. EPA, 1994). The interference sources include: 1) spectral interferences caused by the absorbance of light by a molecule or atom different from the analyte of interest; 2) matrix interference inhibiting the atomization cycle; 3) specific element interference; and 4) memory interference resulting from analysis of a sample containing a high concentration of an element that is not quantitatively removed in the furnace step.

Standard method SM 3113 B has also been approved for analysis of selenium using electrothermal atomic absorption (APHA et al. 1992, 1995, 2005). The optimum selenium concentration range reported for SM 3113 B is 5–100 µg/L, and the estimated detection level is 2 µg/L (APHA et al., 2005).

Standard method SM 3114 B, a manual hydride generation atomic absorption spectrometry method, is applicable for an optimum selenium concentration range of 2–20 µg/L and has an MDL of 2 µg/L (APHA et al., 2005). This method is applicable to the determination of selenium by conversion to its hydride form by a sodium borohydride reagent and transported into an atomic absorption atomizer. Se(VI) is not measurably reduced by sodium borohydride. To determine selenium the method reduces Se(VI) to Se(IV) by an acid digestion procedure. Se(IV) in the filtered water sample is converted to volatile selenium hydride and transported to an atomic adsorption atomizer where it can be analysed. By using this preparation step to convert Se(VI) to Se(IV), it is possible to distinguish the selenium species in the sample (APHA et al., 2005).

The methods cited in the 22nd edition of *Standard Methods for the Examination of Water and Wastewater* (APHA et al., 2012) are also available for the analysis of selenium.

The ASTM International methods approved by the U.S. EPA are the 1998, 2003 and 2008 versions of ASTM D3859 A and ASTM D3859 B. Both methods utilize atomic absorption procedures. Method A (gaseous hydride atomic absorption spectrometry) is equivalent to SM 3114 B and is applicable within the range from 1 to 20 µg/L. The range reported for method B (graphite furnace atomic absorption spectrometry) is from 2 to 100 µg/L, and this method is equivalent to SM 3113 B.

The current practical quantitation level (PQL), based on the capability of laboratories to measure the concentration of selenium within reasonable limits of precision and accuracy, is 10 µg/L (U.S. EPA, 1991c). Recently, as part of the U.S. EPA's second 6-year review, an assessment of the analytical data for selenium from the Proficiency Testing Program was conducted. The U.S. EPA reported high passing rates for laboratories (greater than 75%) analysing samples at the current PQL. However, because of a lack of analytical performance data below the current value of 10 µg/L, the U.S. EPA has not recommended lowering the current PQL (U.S. EPA, 2009).

A recent experimental method reported an MDL of 0.01 µg/L each for Se(IV) and for Se(VI) in tap water using microwave-induced nitrogen plasma mass spectrometry (Minami et al., 2003).

7.0 Treatment technology and distribution system considerations

Selenium has several oxidation states, but only two are predominant in drinking water: Se(IV) and Se(VI). The chemical speciation and behaviour of selenium are highly dependent on the pH and redox potentials of the environment. In natural water (pH 6.0–9.0) under oxidizing conditions, Se(VI) predominates as the divalent ionic form SeO_4^{2-}. Se(IV) will predominate under reducing conditions; at pH below 8.15, the monovalent biselenite anion $HSeO_3^-$ will be the dominant form; at pH greater than 8.15, the divalent anion SeO_3^{2-} will dominate. Reduced selenium species such as elemental selenium (Se^0) and selenides (HSe^-) are insoluble and likely to be released as colloidal suspensions in the surface water. Organic selenium species occur in the natural water by means of microbiological assimilation and degradation (McKeown and Marinas, 1985; Clifford, 1999).

Control options for addressing selenium in drinking water include blending of waters, selection of alternative low-selenium sources and the removal of excess selenium by treatment

processes at the public water supply or household level. Blending can reduce the equipment capacity requirements and costs by blending or mixing a portion of the feed water with the treated water. However, the initial concentration of selenium in the source water and the efficiency of the treatment process will determine if the blending process is advantageous (U.S. EPA, 1985).

7.1 Municipal scale

The removal of excess selenium from drinking water has not been studied on a full-scale treatment plant basis, and limited data exist on laboratory and pilot plant tests. The speciation of selenium in the raw water plays a critical role in the effectiveness of treatment methods used for the removal of selenium. As the species of selenium will determine the effectiveness of the treatment technologies, the removal of Se(IV) and Se(VI) will be considered separately when applicable.

The U.S. EPA has identified the following technologies as the best available technologies (BATs) for selenium removal from drinking water: coagulation/filtration (for Se(IV) only), lime softening, ion exchange (for Se(VI) only), RO, activated alumina and electrodialysis reversal (for Se(IV) only). The removal efficiency of most of the BATs ranged from 75% to 99%; however, lime softening and electrodialysis reversal achieve lower removal rates of approximately 50% and 71%, respectively (U.S. EPA, 1991c). Although conventional coagulation and lime softening processes demonstrated a limited capacity for removing Se(VI), these two technologies may be used when the removal of Se(IV) is sufficient to meet the guideline value for selenium in drinking water (U.S. EPA, 1989).

Several studies demonstrated that adsorptive materials containing various iron oxides were capable of removing selenium species in the water. Se(IV) has been found to adsorb more readily than Se(VI) (Lo and Chen, 1997; Zingaro et al., 1997; Li and Viraraghavan, 1998; Rovira et al., 2008).

The selection and effectiveness of the treatment process are driven by several factors, including source water chemistry, selenium oxidation state, selenium concentration, pre-existing treatment processes and facilities, treatment goals, residual handling concerns and costs.

7.1.1 Conventional coagulation/filtration and lime softening processes

The removal efficiency of selenium by conventional coagulation/filtration treatment depends on the oxidation state of selenium, coagulant type and dose, the selenium concentration in the raw water and the pH of the treated water (Sorg and Logsdon, 1978; Sorg, 1985). The removal of selenium from drinking water by conventional coagulation processes has not been investigated in a full-scale treatment plant. Jar tests and pilot-scale tests demonstrated that conventional coagulation/filtration techniques are moderately successful in removing Se(IV) (80% removal efficiency) and ineffective in removing Se(VI) from the drinking water supply. Conventional coagulation/filtration and lime softening processes are not defined as BATs for small systems unless these treatment processes are currently in place (U.S. EPA, 1991c).

7.1.1.1 Removal of Se(IV)

Jar tests evaluated the impact of different parameters, such as coagulant type, pH of the raw water and the influent selenium concentration, on the effectiveness of the coagulation process. The optimum treatment conditions have been confirmed by a pilot plant study. Both the bench and pilot scale tests showed that Se(IV) was effectively removed (70-80%) by ferric coagulation whereas alum coagulation was relatively ineffective (10-20% removal).

Jar test experiments demonstrated that the application of a ferric sulphate dose of 25 mg/L achieved an approximately 80% reduction of the spiked Se(IV) concentration (0.03 mg/L) in surface water in the pH range of 6–7. Parallel experiments conducted with groundwater achieved up to 70% Se(IV) reduction. The removal efficiency decreased to approximately 10% when the pH increased to 9 for both types of water (Sorg, 1985).

Alum was found to be independent of pH and less effective (10–25%) than the ferric sulphate coagulant for Se(IV) removal. An alum dose of 25 mg/L achieved up to 25% removal of the 0.03 mg/L spiked Se(IV) in surface water at pH 6–7, whereas the tests conducted with groundwater reported up to 15% removal. Both ferric and alum coagulants achieved greater removal efficiency for Se(IV) in surface water than in groundwater (Sorg and Logsdon, 1978; Sorg, 1985).

Sorg and Logsdon (1978) reported that an increase in selenium removal was achieved by increasing the dose of either coagulant. Jar test experiments demonstrated that increasing the ferric doses at a pH in the range of 8.5–8.6 achieved better removal improvement than at a pH in the range of 5.5–7.0. Conversely, experiments conducted with increased alum doses achieved better improvements in the lower pH range.

To determine the effect of the influent Se(IV) concentrations on the effectiveness of the coagulation process, jar tests were conducted with feed Se(IV) concentrations up to 10 mg/L. Se(IV) removal capacity was decreased from 58% to approximately 30% when the influent Se(IV) concentrations increased from 0.1 mg/L to 10 mg/L using a ferric sulphate dose of 25 mg/L and pH of 7.2 (Sorg and Logsdon, 1978; Sorg, 1985).

In a pilot-scale study, the coagulation/dual-media filtration techniques demonstrated that an average influent Se(IV) concentration of 0.027 mg/L in surface water was reduced to 0.005 mg/L (81% removal) using a ferric sulphate dose of 23 mg/L and pH of 6.9. The removal rate decreased to approximately 30% as the pH increased to 8.3. A ferric sulphate dose of 30 mg/L achieved 79% reduction of a Se(IV) concentration of 0.047 mg/L in groundwater at pH 6.4. Parallel experiments conducted with alum doses in the range of 30–34 mg/L achieved up to 20% removal of the influent Se(IV) concentrations in the range of 0.019–0.03 mg/L in surface water and pH in the range of 6.6–8.3. An alum dose of 28 mg/L reduced an influent concentration from 0.056 mg/L to 0.04 mg/L (29% removal) in groundwater at pH 7.8 (Sorg and Logsdon, 1978; Sorg, 1985).

Co-precipitation involves sorption/inclusion of contaminants to an actively precipitating substrate, resulting in the formation of mixed solid-phase. Surface adsorption is one of the principal mechanisms of co-precipitation. Laboratory experiments investigated the factors affecting the iron/selenium precipitation system, such as the type of precipitant ($FeCl_3$ and $FeSO_4$), pH, mixing time, turbidity and temperature. Because SO_4^{2-} anions showed ability to compete for the adsorption sites, experiments were only conducted and reported for $FeCl_3$. The initial Se(IV) concentration of 0.05 mg/L in synthetic water was reduced by between 83.8 and 93.4% using $FeCl_3$ doses ranging from 5 to 20 mg/L and pH levels between 6 and 8. The optimum mixing time was reported as being between 5 and 10 minutes. The turbidity and temperature of the water ranged widely. A water supply with design output of 2000 m^3/day used the process of iron/selenium co-precipitation to remove selenium from spring water. An influent selenium concentration (the form of selenium was not specified) in the range of 0.03–0.04 mg/L was reduced to below 0.01 mg/L using a ferric chloride dose of 5 mg/L, a mixing time of 10 minutes and a pH of 7 (Shi et al., 2009).

Studies reported that the prechlorination process may affect the removal of Se(IV) in drinking water, as the chlorine will tend to oxidize Se(IV) to Se(VI) (Sorg, 1985; Boegel and Clifford, 1986). Coagulation tests, following a prechlorination process with a chlorine dose of 2

mg/L and pH of 6.4, showed a reduction in Se(IV) removal efficiency from 56% to 21% when the chlorine contact time increased from 0 to 60 minutes. The coagulation process was conducted on spiked well water with a Se(IV) concentration of 0.1 mg/L and a ferric sulphate dose of 25 mg/L. The same trend of decrease was found at pH in the range of 7.9–8.1, but not in the range of 6.8–7.8 (Sorg, 1985). However, Boegel and Clifford (1986) found that the optimum pH for the oxidation of Se(IV) using free chlorine at a concentration of 2 mg/L ranged from 6.5 to 7.5.

7.1.1.2 Removal of Se(VI)

Jar tests and pilot-scale tests demonstrated that conventional coagulation/filtration techniques are ineffective in removing Se(VI) from the drinking water supply. Jar tests conducted with alum and ferric sulphate doses as high as 200 mg/L and at pHs in the range of 6–8 reported less than a 10% removal of Se(VI) from both surface water and groundwater (Sorg and Logsdon, 1978; Sorg, 1985; U.S. EPA, 1985).

Pilot-scale studies, using ferric sulphate and alum coagulants, achieved 11% and 18% reduction of Se(VI) concentration, respectively, in the settled water. The tests were conducted with a ferric sulphate dose of 32 mg/L, an initial Se(VI) concentration of 0.097 mg/L and a pH of 6.5. Tests with the alum coagulant were conducted with an alum dose of 25 mg/L, an initial Se(VI) concentration of 0.028 mg/L and a pH of 6.8 (Sorg and Logsdon, 1978; Sorg, 1985).

7.1.1.3 Lime softening

Jar test and pilot plant lime softening investigations demonstrated that the technology achieved approximately 50% Se(IV) removal and was ineffective for Se(VI). Lime softening is a pH-dependent process.

The maximum Se(IV) removal (range of 45–50%) was observed at pH 11.5, whereas the removal rate decreased to 30% when the pH was decreased to 9.5. An increase of the influent Se(IV) concentration in the range of 0.05–10 mg/L showed that the removal efficiency remained constant at approximately 50% (Sorg, 1985).

The results for Se(VI) removals were similar to those reported for conventional coagulation treatment, achieving a maximum 10% removal at a pH in the range of 9–11.5 with initial Se(VI) concentrations ranging from 0.03 to 10 mg/L (Sorg and Logsdon, 1978; Sorg, 1985; U.S. EPA, 1985).

Pilot plant studies confirmed the jar tests results. Pilot-scale experiments demonstrated approximately 50% and 10% reductions of Se(IV) (0.028 mg/L) and Se(VI) (0.038 mg/L), respectively, at a pH of 11.3. These percentages correspond to calculated reductions of finished water concentrations of 0.013 mg/L for Se(IV) and 0.034 mg/L for Se(VI) in groundwater (Sorg and Logsdon, 1978; Sorg, 1985).

7.1.2 Ion exchange

Ion exchange is a physicochemical process in which there is an exchange of ions in the raw water with ions within the solid phase of a resin. As raw water ions displace ions on the resin, the capacity of the resin is gradually exhausted, resulting in finished water concentrations that increase (i.e., contaminant breakthrough). Once the resin has reached its capacity (i.e., when all the resin sites are occupied by the contaminant ion), the resin must be regenerated to reverse the process. The presence of organic contaminants, suspended solids, calcium or iron can cause fouling of the ion exchange resins.

Removal efficiency of greater than 80% is considered to be achievable by strong base anion (SBA) exchange resins for selenium in drinking water (U.S. EPA, 1990b, c). Factors affecting selenium removal by ion exchange include the oxidation state of selenium, the

concentration of competing anions and the type of the selected resin. Selenium is usually present at trace concentrations in the drinking water, and the efficiency of its removal is controlled by the concentrations of common drinking water anions, such as sulphate, nitrate, chloride and bicarbonate. The ion exchange behaviour of Se(IV) was found to be similar to that of nitrate, whereas the behaviour of Se(VI) was identical to that of sulphate (Maneval et al., 1985). However, Boegel and Clifford (1986) found that nitrate was preferred over Se(IV) and that Se(VI) was clearly preferred over sulphate. Pilot studies should be conducted in order to verify the effectiveness of ion exchange technology for site-specific water quality.

7.1.2.1 Removal of Se(IV)

The low position of the Se(IV) ion in the ion selectivity sequence suggests that ion exchange is not favourable for Se(IV). The strong-base anion exchange resins have less preference for Se(IV) anions in comparison with Se(VI), nitrate and sulphate (Maneval et al., 1985; Boegel and Clifford, 1986; Li and Viraraghavan, 1998). Another factor affecting the ion exchange removal of Se(IV) is the pH of the treated water. The ion exchange behaviour of the monovalent biselenite form ($HSeO_3^-$) and divalent form (SeO_3^{2-}) should be considered, as the monovalent anion is less preferred than the divalent anion (Maneval et al., 1985).

Clifford (1999) indicated that "chromatographic peaking" of Se(IV) may occur. Chromatographic peaking is a process in which less preferred ions will be concentrated in the column and will, at some time, exit the column in concentrations exceeding their influent concentrations. A laboratory ion exchange column treated mineralized synthetic groundwater containing total dissolved solids at a concentration of 712 mg/L, sulphate at a concentration of 192 mg/L and Se(IV) at a concentration of 0.1 mg/L. The strong-base anion exchange unit achieved a Se(IV) concentration of 0.01 mg/L, with run lengths of 152 bed volumes and an empty bed contact time of 5 minutes. Chromatographic peaking of 0.54 mg Se(IV)/L (5.4 times the feed concentration) occurred at 237 bed volumes (Boegel and Clifford, 1986).

A laboratory experiment using strong-base type I quaternary anion exchange resin was capable of reducing the Se(IV) concentration from 0.1 mg/L to 0.01 mg/L with run lengths of 238 bed volumes, and an adsorption capacity of 23.3 mg Se(IV) per litre of media. Although empty bed contact time (EBCT) was not provided in the published article, this article was based on the author's thesis (Li, 1998), which stated an EBCT of approximately 2.87 minutes. The resin was exhausted after 18 hours of operation, achieving 371 bed volumes and adsorption capacity of 31.9 mg per litre of media. The experiment was conducted with spiked tap water and in the presence of 366 mg/L sulphate concentration (Li and Viraraghavan, 1998; Li, 1998). Although the authors have not observed chromatographic peaking, it is a major operational consideration when using anion exchange for Se(IV) treatment. Chromatographic peaking causes the effluent Se(IV) concentration to be greater than the influent concentration due to the presence of sulphate and nitrate ions, which displace Se(IV) ions on the resin (Clifford, 1999).

Modified cation exchange resins and chelating resins have been used for Se(IV) removal. Maneval et al. (1985) showed that a weak acid cation resin loaded with ferric ions could be used to remove selenite from water containing sulphate and chloride ions. In a later in-depth study laboratory tests using chelating polymer resin with immobilized copper(II) ions in the solid phase showed a high affinity towards Se(IV) anions, over Se(VI), sulphate and chloride anions. A fix-bed ion exchange column reduced a Se(IV) concentration to below 0.01 mg/L from an influent concentration of 2 mg/L in the presence of Se(VI) at a concentration of 2 mg/L, sulphate at a concentration of 100 mg/L and chloride at a concentration of 200 mg/L, at pH 9.5 and with an empty bed contact time of 0.21 hour (12.6 minutes). The experiments demonstrated that the ion exchange resin selectively reduced the Se(IV) concentration, as it achieved greater than 1000

bed volumes of treated water for Se(IV) and 200 bed volumes for Se(VI) (Ramana and Sengupta, 1992). Although the authors indicated that regeneration of the resin is possible using brine or sodium carbonate, regeneration and reuse of copper loaded chelating resin may be challenging.

7.1.2.2 Removal of Se(VI)

Strong-base anion exchange resins demonstrated greater removal efficiency for Se(VI) than for Se(IV) (Boegel and Clifford, 1986; Li and Viraraghavan, 1998). However, the effectiveness of the Se(VI) removal is limited by the presence of sulphate ions, as the affinity of sulphate is nearly as great at that of Se(VI), and sulphate, typically present in a much higher concentration, compete strongly with Se(VI), for ion exchange sites-(Maneval et al., 1985; Boegel and Clifford, 1986). Boegel and Clifford (1986) predicted that the number of bed volumes that can be treated before Se(VI) breakthrough occurs may increase when the sulphate concentration is decreased. An increase of greater than 700 bed volumes was expected when a strong-base anion resin treated source water containing sulphate at a concentration of 50 mg/L in comparison with a sulphate concentration of 192 mg/L.

Pilot-scale experiments using a SBA exchange resin, primarily developed for selective nitrate removal in drinking water, showed a high affinity towards Se(VI) anions (Cousin et al., 2011). The experiments reported that the removal of selenium was concurrent to the removal of the competing sulphate and chloride anions. The authors also reported results for Se(VI) removal with both fresh and regenerated resin. Data indicated that after the second regeneration cycle, the SBA exchange resin was capable of reducing an influent Se(VI) concentration in groundwater from 30.1µg/L to 0.5 µg/L with run lengths of 920 bed volumes, while the nitrate concentration was reduced from approximately 20 mg/L to 3.44 mg/L.. The Se(VI) concentrations in the water samples treated by SBA exchange resin increased gradually over time and ranged from below 0.5 µg/L after 64 hours (920 bed volumes) to 8.3 µg/L after 84 hours of treatment (1240 bed volumes). The nitrate concentration in the samples increased from 3.44 mg/L to 16.8 mg/l after 84 hours (1240 bed volumes) (Cousin et al., 2011).

Laboratory experiments evaluated a SBA resin in chloride form for the removal of Se(VI) from mineralized synthetic water containing total dissolved solids at a concentration of 712 mg/L and sulphate at a concentration of 192 mg/L. The ion exchange column treated influent Se(VI) concentrations ranging from 0.1 mg/L to 0.01 mg/L, achieving run lengths of 235 bed volumes. The ion exchange column operated at a pH of 8.3 and an empty bed contact time of 5 minutes. Se(VI) was eluted after the sulphate ions and was not subject to chromatographic peaking (Boegel and Clifford, 1986). Another laboratory experiment found that a strong-base type I anion exchange resin was capable of reducing the Se(VI) concentration from 0.1 mg/L to 0.01 mg/L with run lengths of 361 bed volumes, achieving an adsorption capacity of 36.3 mg Se(VI) per litre of media. Although empty bed contact time (EBCT) was not provided in the published article, this article was based on the author's thesis (Li, 1998), which stated an EBCT of approximately 2.87 minutes.The resin was fully exhausted after 28 hours of operation, achieving 595 bed volumes and adsorption capacity of 52.3 mg Se(VI) per litre of media. The experiment was conducted with spiked tap water and in the presence of 366 mg/L sulphate concentration (Li and Viraraghavan, 1998).

Based on laboratory experiments, Clifford (1999) suggested that an ion exchange process in combination with an oxidation pretreatment step of Se(IV) to Se(VI) may be considered as a technically feasible process. A free chlorine concentration of 2 mg/L achieved a 60% oxidation of Se(IV) within 5 minutes at a pH in the range of 6.5–8.0. However, at pH 9, only 15% of Se(IV) could be oxidized in 5 minutes. In this study, hydrogen peroxide and potassium

permanganate were found to be less effective, whereas oxygen was found to be ineffective (Clifford, 1999).

A consideration when using strong-base anion exchange resins is the potential for the release of nitrosamines from the resin. Kemper et al. (2009) found that new resin or resin that is exposed to disinfectants (chlorine and chloramines) may release nitrosamines due to shedding of manufacturing impurities. To minimize nitrosamine formation, attention should be paid when selecting strong-base ion exchange resins (Kimoto et al., 1980; Najm and Trussell, 2001).

7.1.3 Membrane processes: reverse osmosis

RO technology is based on forcing water across a membrane under pressure while the ionic species, such as Se(IV) and Se(VI), are retained in the waste stream. The performance of the RO membrane systems depends on a variety of factors, including the quality of the raw water, the type of the membrane, molecular weight cut-off and recovery of the system (Jacangelo et al., 1997). The presence of iron, manganese, silica, scale-producing compounds and turbidity could negatively affect the system performance. A pretreatment of the feed water is required to prevent scaling and fouling of the RO membranes. The product water typically requires post-treatment, consisting of pH and alkalinity adjustments.

RO technology has been shown to be an effective method for the removal of selenium from drinking water. Pilot-scale studies demonstrated that RO may achieve removal efficiency in the range of 75–99% (Sorg et al., 1980; U.S. EPA, 1985, 1989; Huxstep and Sorg, 1988) for selenium in drinking water, and the technology is typically used when high concentrations of other dissolved solids need to be removed (U.S. EPA, 1989). As RO systems generally produce high-quality water, the blending of treated water and raw water to produce finished water of acceptable quality may be a factor in selecting an RO system (U.S. EPA, 1985).

Eight RO systems with varied design capacities in the range from 800 to 1 million gallons per day (Mgd) (0.003–3.8 ML/day) have effectively reduced selenium concentrations in groundwater. The systems used hollow fibre and/or spiral wound cellulose acetate membranes, supplied by six different manufacturers. Data from RO systems with a capacity ranging from 0.115 to 3.8 ML/day indicated that the selenium concentrations in the range of 0.014–0.025 mg/L were lowered to below the detectable level (0.005 mg/L). These systems operated with design water recovery in the range of 50–75% and a feed pressure of 2800–2900 kPa (400–425 psi). Smaller systems (0.003–0.019 ML/day) having a design water recovery of 35–50% and a feed pressure of 1400–2800 kPa (200–400 psi) achieved a finished water concentration below the detectable level (0.005 mg/L) from a feed concentration in the range of 0.015–0.025 mg/L. All treatment configurations consisted of pretreatment of the raw water, RO unit and post-treatment. Pretreatment included filtration, pH adjustment to 6.0–6.2 as well as calcium and magnesium sequestration. Post-treatment consisted of pH adjustment, degassing and disinfection (Sorg et al., 1980).

Pilot-scale testing evaluated the effectiveness of five different RO membranes for the rejection of inorganic contaminants. Each membrane has been tested according to the manufacturer's specifications. The feed water pressure, water recoveries and product water flow rates differed between membrane elements. The investigations demonstrated a high rejection rate in the range from 95% to 99% and from 98% to greater than 99% for Se(IV) and Se(VI), respectively, under a variety of operating conditions. The reported influent concentrations ranged from 0.33 to 1.5 mg/L for Se(IV) and from 0.61 to 2.7 mg/L for Se(VI) (Huxstep and Sorg, 1988).

Considerations when using RO treatment include disposal of the reject water and possible increased corrosivity of the treated water (Schock and Lytle, 2011). RO rejects a significant

portion of the influent water as contaminant-rich brine (Taylor and Wiesner, 1999), and the concentrate discharge must be disposed of appropriately. The removal of contaminants can cause mineral imbalances that could increase the corrosive nature of the treated water (Schock and Lytle, 2011). In most cases, post-treatment corrosion control measures need to be undertaken.

7.1.4 Adsorption

7.1.4.1 Activated alumina

The removal of selenium from drinking water by activated alumina has been investigated on a laboratory basis. Activated alumina treatment demonstrated a selenium removal in the range of 85–95%. However, the feasibility of the treatment process depends on the selenium species in the raw water, as the activated alumina preferentially adsorbs Se(IV) (U.S. EPA, 1985, 1989).

Activated alumina is a physicochemical process by which ions in the feed water are sorbed to the oxidized activated alumina surface. Activated alumina is used in packed beds, which may operate in series or parallel. Feed water is continuously passed through the packed bed. The contaminant ions in the water are exchanged with the surface hydroxides on the alumina. When adsorption sites on the activated alumina surface become filled, the bed must be regenerated. Regeneration of activated alumina is accomplished through a sequence of rinsing with regenerant (sodium hydroxide), flushing with water and neutralizing with acid, such as sulphuric acid for Se(IV) recovery and hydrochloric acid for Se(VI) recovery (U.S. EPA, 1998).

Studies have shown that activated alumina is an effective treatment technique for the removal of inorganic contaminants, including arsenic, selenium, fluoride and silica. As a result of the amphoteric nature of activated alumina, the adsorption process is influenced by pH. Below pH 8.2 (a typical zero point charge for activated alumina), the activated alumina surface has a net positive charge, and it will adsorb anions found in the water (Clifford, 1999). Factors such as pH, contaminant oxidation state, regenerant dose and flow rate, competing ions and empty bed contact time can influence the inorganic contaminant removal by activated alumina. When employing activated alumina technology, operational issues that must be considered include the degradation of activated alumina through the regeneration process and the fouling of the activated alumina bed, resulting in an increase in headloss across the media bed. The activated alumina process also has the potential for "chromatographic peaking" where the effluent selenite concentration would exceed its influent concentration due to the presence of more preferred ion such as fluoride or phosphate in the influent water.

Activated alumina may not be suited for small systems because of the special operational requirements. The technology requires adequate surveillance and maintenance, including the use of concentrated acids (sulphuric acid or hydrochloric acid) and base (sodium hydroxide) for regeneration of activated alumina. These can be hazardous, particularly if the operator's knowledge and skills are insufficient for handling hazardous materials. Utilities need to consider the chemical handling and disposal requirements prior to selecting this treatment technology (U.S. EPA, 1989, 1998).

Adsorption of Se(IV)

A laboratory-scale continuous-flow column of activated alumina studied the removal efficiency of Se(IV) from synthetic well water (Trussell et al., 1980). The study developed activated alumina breakthrough capacities for three different influent Se(IV) concentrations, pH in the range of 5–7 and a surface loading rate of 3 gpm/ft^2 (7.3 m/h) and an EBCT of 1.87 min which can be calculated for the 9 inch deep column and the flow rate used, in the study. The breakthrough capacity has been defined as the amount of selenium adsorbed per litre of activated

alumina before the effluent selenium concentration exceeded the treatment goal of 0.01 mg/L. Trussell et al. (1980) reported the following breakthrough capacity for activated alumina:

pH	Influent Se (IV) concentrations			Bed Volumes
	0.05 mg/L	0.1 mg/L	0.2 mg/L	
	Breakthrough capacity (mg Se(IV)/L activated alumina)			
5	60	120	235	1200
6	45	90	175	900
7	25	50	100	500

Activated alumina showed optimum adsorption capacity for Se(IV) at pH in the range of 5–6, and the capacity of the media was proportional to the initial selenium concentration in the raw water. The study investigated the impact of various ions on the adsorption efficiency of Se(IV) by activated alumina. Whereas bicarbonate ions had the more pronounced effect on Se(IV) adsorption, chloride, nitrate and sulphate ions showed only marginal interference. Based on the graphical representation of the experimental data, an increase in bicarbonate concentration from 50 to 200 mg/L reduced the removal efficiency of Se(IV) by approximately 10% at a pH in the range of 6.0–6.5. Calcium, magnesium and sodium cations, at concentrations as high as 200 mg/L, did not have a negative impact on the adsorption of Se(IV).

Activated alumina was regenerated with 0.5% sodium hydroxide at a flow rate of 0.5 gpm/ft^2 (1.2 m/h). The regenerant's flow rate demonstrated a great effect on Se(IV) recovery and its subsequent removal. Experiments showed that the percent recovery of Se(IV) during the regeneration was increased twice when the regenerant flow rate was decreased from 1.0 gpm/ft^2 to 0.5 gpm/ft^2 (2.4 to 1.2 m/h) EBCT (calculated from the information provided n the study), increased from 5.6 minutes to 11.2 minutes for 9 inch deep column.

Adsorption of Se(VI)

As Se(VI) has a low position in the selectivity series of activated alumina, it is more susceptible to interference with adsorption. The experiments found that the adsorption capacity of activated alumina with respect to Se(VI) was approximately 1/13th of the capacity for Se(IV) under similar conditions (Trussell et al., 1980; Kreft, 1985).

Sulphate ions strongly interfered with Se(VI) removal by activated alumina. Trussell et al. (1980) reported that the number of bed volumes that can be treated before Se(VI) breakthrough occurs may decrease significantly when sulphate is present. An increase of the sulphate concentration from 5 to 500 mg/L would decrease the bed volumes of the treated water from 450 to 15 at pH 6. These capacities have been reported for an influent Se(VI) concentration of 0.05 mg/L in the presence of a bicarbonate concentration of 100 mg/L. At a low ratio of sulphate to Se(VI), the adsorption capacity of the activated alumina for Se(VI) was increased. Similar tests showed that the effect of bicarbonate concentration was not as great as that of sulphate. An increase of the bicarbonate concentration from 5 to 500 mg/L decreased the bed volumes of the treated water from 125 to 33 at pH 6. Alkalinity tests have been conducted for an influent Se(VI) concentration of 0.05 mg/L and sulphate concentration of 100 mg/L. Chloride and nitrate ions had no pronounced effect on Se(VI) adsorption. Sodium, magnesium and calcium, at concentrations as high as 200 mg/L for each, did not negatively affect the adsorption of Se(VI). The study found that the calcium and magnesium concentrations may slightly enhance the adsorption of Se(VI), due to the "secondary adsorption" phenomenon. Secondary adsorption occurs as a joint adsorption of anions with multivalent cations or as a joint adsorption of cations with multivalent anions (Trussell et al., 1980).

A laboratory-scale study was conducted using a continuous-flow column of activated alumina, treating synthetic well water to Se(VI) levels of 0.01 mg/L with run lengths of 100, 70 and 35 bed volumes (adsorption capacities of 4.5, 3.2 and 1.6 mg/L alumina, respectively), at pHs of 5, 6 and 7, respectively. The treatment goal of 0.01 mg/L was achieved by treating an influent Se(VI) concentration of 0.05 mg/L in the presence of sulphate anions at a concentration of 100 mg/L. The study used 0.5% sodium hydroxide for the regeneration of activated alumina at a flow rate of 2 gpm/ft^2 (4.8 m/h) and hydrochloric acid for the neutralization of the bed (Trussell et al., 1980).

7.1.5 Electrodialysis/electrodialysis reversal

Electrodialysis is an electrochemical separation process in which charged species from water are transported through semipermeable membranes under the influence of an electric potential. The membranes are configured in "stacks" parallel to one another, and each successive membrane carries direct electric current. Cations and anions migrate through the cation and anion membranes, respectively. In electrodialysis reversal, the polarity of the electrodes is changed periodically across the ion exchange membranes, causing a reversal in ion movement. This step minimizes the scale build-up on the membranes, and thus electrodialysis reversal can operate for a longer period of time between cleaning. Electrodialysis is generally automated and allows for part-time operation, and it may be an appropriate technology for small systems (U.S. EPA, 1998).

A field test reported that a selenium concentration of 0.05 mg/L in the groundwater was reduced to 0.002 mg/L. No information was provided on the operational conditions of the electrodialysis systems (U.S. EPA, 1985). Data from two mobile units treating public water supply demonstrated that electrodialysis reversal was capable of reducing selenium concentrations in source water. This study demonstrated an average selenium reduction of 71% from an influent concentration in the range of 0.005–0.0075 mg/L in well water. The pretreatment of the raw water included carbon filtration (Folster et al., 1980; U.S. EPA, 1991c).

Utilities planning to utilize electrodialysis for the reduction of selenium, total dissolved solids and other trace metals would require pilot plant testing of the feed water in order to verify the effectiveness of selenium removal.

7.1.6 Manganese greensand filtration

The active component in "greensand" is glauconite, a green, iron-rich mineral that has ion exchange properties. In manganese greensand filtration, the soluble metals in the water, such as iron and manganese, are oxidized and precipitated when they come in contact with oxides of manganese on the greensand granules. When the manganese greensand bed is exhausted, the bed is regenerated to restore its oxidizing capacity.

Laboratory column tests (Li and Viraraghavan, 1998) studied the efficiency of manganese greensand filtration for the removal of Se(IV) and Se(VI) from spiked tap water. The column was capable of reducing the feed water Se(IV) concentration of 0.1 mg/L to 0.01 mg/L (90% removal), achieving an adsorption capacity of 1.73 mg/L media. It was found that the addition of ferric chloride to the raw water enhanced the removal of Se(IV). Selenium(IV) adsorption capacities of 2.37 and 3.2 mg/L of media have been reported when the iron to Se(IV) ratios were 10:1 and 20:1, respectively. The process has been reported to be ineffective for Se(VI) (Li and Viraraghavan, 1998).

7.1.7 Emerging treatment technologies

Emerging treatment technologies include the following:

- *Iron based materials:* Granular ferric hydroxide (GFH) is an iron based adsorptive media currently used for treatment of arsenic in drinking water. Full-scales GFH media-based systems for arsenic removal reported that the media was capable of removing selenium in drinking water. However, no operational data for selenium have been reported (Cumming et al., 2007).
  Ferric oxide media is an iron based media that adsorbs arsenic and other ions including selenium (U.S. EPA, 2005). Effective adsorption occurs at pH values ranging between 6.0 and 8.0. At pH values greater than 8.0 to 8.5, pH adjustment is recommended to ensure adsorption capacity is maintained. Silica and phosphate are the competing ions that can reduce the adsorption capacity. No operational data for selenium have been reported for selenium removal.
  Several researchers have studied iron oxide–coated sand (Lo and Chen, 1997; Li and Viraraghavan, 1998), aluminum oxide–coated sand (Kuan et al., 1998) and natural iron oxides (Zhang and Sparks, 1990; Rovira et al., 2008) for the removal of selenium from water. The studies reported that both selenium species had a different degree of adsorption on the iron and aluminum oxides and that Se(IV) was found to adsorb more readily than Se(VI).
  A laboratory column study found that selenium removal by iron oxide–coated sand was possible for Se(IV). The study demonstrated a 90% reduction of a Se(IV) concentration of 0.1 mg/L in spiked tap water, achieving an adsorption capacity of 2.7 mg Se(IV)/L of media. However, the process was reported as being ineffective for Se(VI) (Li and Viraraghavan, 1998). Lo and Chen (1997) reported practically complete removal of Se(IV) with an initial concentration of 10 mg/L after 10 minutes in contact with 100 g/L iron oxide–coated sand. Se(VI) removal required approximately 90 minutes for a similar reduction at the same initial concentration. The authors reported a Se(IV) adsorption capacity in the range of 0.014–0.017 mmol/g and 0.013–0.014 mmol/g for iron oxide–coated sand (Lo and Chen, 1997). In laboratory experiments, iron(II) hydroxide was capable of reducing an influent selenium concentration of 0.004 mg/L to below 0.001 mg/L at pH 8.8 (Zingaro et al., 1997). Another experiment, using aluminum oxide–coated sand, was conducted for the removal of selenium from water. The study reported an adsorption capacity of approximately 0.5 mg/g media for Se(IV) and 0.23 mg/g media for Se(VI) at pH in the range of 7.18–8.3 (Kuan et al., 1998).
- *Adsorption with polymer–clay composite*: Several polymer–clay composites have been designed and tested for selenium removal from water. An adsorption capacity of 18.4 mg Se(VI) per gram media was obtained for a chitosan–clay composite. The composite showed selectivity towards selenium in the presence of sulphate and was able to reduce a Se(VI) concentration of 0.64 mg/L in groundwater to below 0.01 mg/L (Bleiman and Michael, 2010).
- *Dissimilatory reduction*: Biological treatment uses microorganisms to reduce, oxidize or eliminate groundwater contaminants, either as the sole treatment technique or combined with other conventional physicochemical processes, such as sorption and filtration. The basic principle of the biological treatment is that remediation takes place as the result of oxidation–reduction potential changes (Zouboulis and Katsoyiannis, 2005). The metabolism of dissimilatory metal-reducing microorganisms may reduce uranium, selenium, chromium and possibly other metals to insoluble forms that can be removed from contaminated waters (Lovley, 1995).

7.1.8 Distribution system materials: non-leaded brass alloys

Typically, non-leaded brass alloys contain lead in the range of 0.1–0.25% by weight as an incidental impurity from the recycled materials or ores used as the source metals. Metals such as

bismuth and selenium are added to the alloys to replace the lead and improve the mechanical characteristics. Data on the potential of non-leaded brass to leach metals such as selenium are limited, and additional studies need to be undertaken in order to gain a better understanding of the leaching propensity of these alloys.

Sandvig et al. (2007) synthesized the current state of knowledge related to the use of non-leaded brass components in drinking water, identified and prioritized recommended research needs related to non-leaded brass and provided a preliminary structure for the highest-priority projects to meet these needs. Based on this report, the Water Research Foundation considered the potential of the non-leaded brass alloys to leach metals, including selenium, as one of the highest-priority research needs.

Sandvig et al. (2012) compared the leaching characteristics of typical utility service connections and premise plumbing devices under the relevant NSF/ANSI 61 Standard test conditions. The objective of the study was to determine whether the current testing conditions set out in the standard for use with chlorinated water can also be used to accurately reflect the release of metals (including lead, copper and selenium) in chloraminated water with sufficient accuracy to meet the public health and regulatory needs of utilities. The project also evaluated the leaching of other metals, including selenium, from leaded- and non-leaded brass devices (e.g., ball valve, corporation stop, water meter, kitchen faucet). Six different types of the devices (triplicate samples), were tested under Section 8 of the NSF/ANSI 61 Standard with 11 types of source water. The normalized metal data showed that selenium was detected in only one sample (0.8 µg/L) of the 198 samples analyzed (reported detection level was 0.5 µg/L). Four different types devices (triplicate samples) were tested under Section 9 of the NSF/ANSI 61 Standard with 8 types of source water. The normalized metal data indicated that selenium was not detected in any of the 96 samples analyzed (reported detection level in the range 0.2 – 2 µg/L).

A Water Research Foundation project (No. 4191) identified and prioritized key water quality characteristics and changes that might adversely impact non-leaded brasses and increase their leaching in drinking water distribution systems. Five different water qualities, including both surface water and groundwater of varying alkalinity, hardness, total organic carbon, pH and secondary disinfectant, were used to study the suitability of non-leaded brass materials for use in drinking water. Preliminary results showed no leaching of selenium in the four non-leaded brass materials tested, indicating that they are suitable for use in drinking water of various water qualities (Turković et al., 2014).

Preliminary tests studied the corrosion and dezincification behaviour and the metal leaching of non-leaded brasses (Peters, 1995; Twarog, 1995; Maas et al., 2002; DeMarco, 2005). Twarog (1995) quantified the leaching levels for two different non-leaded compositions in brasses (2% bismuth/1% selenium and 1% bismuth/0.5% selenium) and compared the results with the control standard alloy (C84400). The tested specimens were hollow cylinders in the "as-cast" condition. The experiments were conducted with synthetic water following the NSF/ANSI Standard 61 section 9 methodology (version was not specified). Three samples of each experimental alloy were tested at pH 5, and three samples were tested at pH 10. The control samples showed that the 19th-day mean normalized leached selenium concentrations were below the detection limits at both pH levels (detection limit was not stated). All experiments conducted with both experimental alloys at pH 5 indicated that the 19th-day mean normalized leached selenium concentrations were below the detection limits. Several of the experiments conducted with both experimental alloys at pH 10 reported that the 19th-day mean normalized leached selenium concentrations were in the range of 0.23–54.56 µg/L. The results indicated a correlation between the levels of selenium leached and the amount of the bismuth in the tested alloys. Selenium concentrations measured in the water samples were less than 10 µg/L when the

bismuth to selenium ratio was 2:1 or greater in the non-leaded brass compositions. Verification tests conducted at pH 8 (NSF/ANSI Standard 61 section 9, 1994 draft) reported that the 19th-day mean normalized leached selenium concentrations were 1.7 µg/L for 2% bismuth/1% selenium alloy, 0.1 µg/L for 1% bismuth/0.5% selenium alloy and below 0.1 µg/L for the control brass alloy C83600 (Twarog, 1995).

Another experiment was conducted with bismuth/selenium–modified cast red brass alloy containing 0.016% lead, 2.23% bismuth and 1.02% selenium. The tested specimens were large faucet body castings. According to the report, the 19th-day mean normalized leached selenium concentrations were below the NSF's maximum allowable level, at that time, of 12.5 µg/L. The test protocol used in the study was not specified (Peters, 1995).

Recent laboratory experiments have been conducted to quantify the levels of the metal leached from two commercially available non-leaded brass alloys: Envirobrass® I and Envirobrass® II. Envirobrass® I alloy may contain selenium in the range of 0.35–0.75%, bismuth from 0.5% to 1.15% and lead at 0.25%, and Envirobrass® II may contain selenium in the range of 0.8–1.1%, bismuth from 1.6% to 2.2% and lead at 0.25%. The tests were conducted with two different leaching solutions: a synthetic test water (NSF/ANSI Standard 61 section 9 methodology) and a solution identified as aggressive for lead leaching from brass alloys. Selenium concentrations leached from these alloys were below the detection limit of 2.98 µg/L for both tested leaching solutions (Triantafyllidou and Edwards, 2006).

7.1.9 Selenium in the distribution system

Contaminants may enter the distribution system through a variety of mechanisms: 1) in a dissolved state from the source water; 2) attached to turbidity particles; 3) added to the source water from the treatment techniques; and/or 4) as by-products of corrosion of piping and plumbing material. The fate and transport of the contaminants and their subsequent accumulation and release within the distribution system are complex processes controlled by a number of chemical, physical and microbial mechanisms. Inorganic contaminants may accumulate on or within materials commonly found in the water distribution system, such as scales, biofilms or sediments, and may be released back to the distribution system water (Schock, 2005; U.S. EPA, 2006).

Case studies, based on available published literature, characterized the potential for the accumulation and release of inorganic contaminants in the distribution system. Schock (2005) found that the scale material from a lead service line contained selenium at concentrations of 0.3, 0.5, 1 and 7.8 mg/kg. However, the stability of the metals accumulated in the scales is unpredictable, and their concentration in the bulk water is not quantifiable.

7.2 Residential scale

Generally, it is not recommended that drinking water treatment devices be used to provide additional treatment to municipally treated drinking water. In cases where an individual household obtains its drinking water from a private well, a residential drinking water treatment device may be an option for reducing selenium concentrations in drinking water. The treatment processes that are capable and able to be certified for selenium removal at the residential scale include adsorption, reverse osmosis (RO) and distillation.

Before a treatment device is installed, the well water should be tested to determine general water chemistry and to verify the concentration of selenium. The testing should also include assessing the presence and concentration of competing ions (e.g., sulphate, nitrate, chloride) and organic matter in the water, which could interfere with selenium removal. Devices can lose removal capacity through usage and time and need to be maintained and/or replaced.

Consumers should verify the expected longevity of the components in their treatment device as per the manufacturer's recommendations.

Health Canada does not recommend specific brands of drinking water treatment devices, but it strongly recommends that consumers use devices that have been certified by an accredited certification body as meeting the appropriate NSF/ANSI drinking water treatment unit standards. These standards have been designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. Currently, there are certified devices for the reduction of selenium from drinking water that rely on RO and distillation treatment processes.

Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards (SCC, 2014):

- Canadian Standards Association International (www.csa-international.org);
- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- Underwriters Laboratories Inc. (www.ul.com);
- Quality Auditing Institute (www.qai.org);
- International Association of Plumbing & Mechanical Officials (www.iapmo.org).

An up-to-date list of accredited certification organizations can be obtained from the SCC (www.scc.ca).

Water treatment technologies able to be certified to NSF standards for reduction of selenium include adsorption, RO and distillation. Applicable standards are NSF/ANSI Standards 53, 58 and 62.

Treatment devices to remove selenium from untreated water (e.g., a private well) can be certified for either the removal of selenium alone or the removal by surrogate testing.

Drinking water treatment devices certified to NSF/ANSI Standards 53, 58 and 62 specifically for selenium removal, must be capable of reducing the concentration of selenium in water from an influent (challenge) concentration of 0.1 mg/L (added as 0.05 mg/L for Se(IV) and 0.05 mg/L for Se(VI)) to a maximum final (effluent) concentration of 0.05 mg/L (NSF/ANSI, 2009a,b, 2011b). However, treatment devices certified to NSF/ANSI Standard 62 to remove selenium can be certified either specifically for selenium as noted above or for the removal of total dissolved solids (TDS) which is used as a surrogate for selenium in this standard. Treatment devices certified to NSF/ANSI Standard 62 using TDS as a surrogate, must achieve a minimum TDS reduction of 99.0% from an influent (challenge) concentration of 1000 mg/L(NSF/ANSI, 2009b).

RO systems certified to NSF/ANSI Standard 58 (Reverse Osmosis Drinking Water Treatment Systems) are intended for point-of-use installation only. RO requires larger quantities of influent water to obtain the required volume of drinking water, because these systems reject part of the influent water. A consumer may need to pretreat the influent water to reduce fouling and extend the service life of the membrane.

Distillation systems certified to NSF/ANSI Standard 62 (Drinking Water Distillation Systems) are also intended for point-of-use installation only. The distillation process is effective for the reduction of inorganic contaminants, but requires an electrical energy input.

NSF/ANSI Standard 61 (Drinking Water System Components—Health Effects) limits the leaching of selenium into drinking water. The standard ensures that materials meet health-based leaching requirements and are safe for use in potable water applications. When materials are

certified to the standard, the concentration of selenium must not exceed the single product allowable concentration of 0.005 mg/L (NSF/ANSI, 2011a).

8.0 Kinetics and metabolism

8.1 Absorption

Very little quantitative information is available on the absorption of selenium compounds through the lungs or skin. Oral absorption via the intestine is the major route of uptake of selenium into the body (Thiry et al., 2012). In laboratory animals and humans, most organic (selenomethionine and selenocysteine) and inorganic (selenite and selenate) forms of selenium are readily absorbed along the ileum and duodenum (Patterson and Levander, 1997; Fairweather-Tate et al., 2010; U.S. EPA, 2010). The form of the element, the amount of selenium in the body and the presence of certain amino acids and sulphur compounds or heavy metals such as mercury in the gut influence the absorption rate (Patterson and Levander, 1997; IPCS, 2006). Elemental selenium and selenosulphide species are poorly absorbed (U.S. EPA, 1991a). Organic selenium is subject to active transport, whereas selenite undergoes passive diffusion in the gut. Selenate is absorbed through the small intestine via the sodium-dependent transporter of sulphate.

In a kinetic comparison study, two 150 µg doses of selenomethionine or selenite were given to healthy American adults with normal plasma selenium concentrations (80–160 µg/L). The absorption of selenomethionine was 97%, whereas that of selenite was around 60% (Wastney et al., 2011). The results of this study were confirmed in another interventional study in the United States (Burk et al., 2006). Selenomethionine increased plasma selenium levels twice as efficiently as selenite at the same doses (200, 400 or 600 µg). Oral absorption of selenite given as a single dose of 81.7 µg has been measured at higher levels (89%) in healthy males (Martin et al., 1988). The composition of the diet was thought to influence absorption.

Oral ingestion of 1700 mg of selenite in humans generated a plasma concentration of selenium of 2.7 mg/L 3 hours after ingestion (generally, blood concentrations are 0.060–0.150 mg/L) (Gasmi et al., 1997).

Selenite is poorly absorbed in ruminants because of the reducing environment of the rumen (Wright and Bell, 1966; Gunter et al., 2003). In general, organic compounds are better absorbed in ruminants and are converted to selenoproteins (Gunter et al., 2003). Selenate and selenite added at 0.3 mg/kg of dry food were absorbed in equal amounts by sheep, cattle and horses, and both induced an increase in blood selenium concentration (Podoll et al., 1992).

Inhalation of selenium-containing aerosols that are not soluble in water have been reported in occupational exposures, such as workers in copper smelters or selenium rectifier plants (U.S. EPA, 2010), but it will not be considered further, as it is not relevant to drinking water. Dermal absorption did not occur in mice or humans exposed to selenium sulphide or selenomethionine (ATSDR, 2003).

8.2 Distribution

Once in the bloodstream, selenium is distributed throughout the body. Most of the absorbed portion of selenite, selenomethionine and selenocysteine is transported to organs with a high rate of selenoprotein synthesis: liver, muscle, brain and, to a lesser extent, testis and kidneys (Deagen et al., 1987; Willhite et al., 1992; Thiry et al., 2012). The remaining selenium stays in plasma or enters the lymphatic tissues before being distributed to other organs (Wastney et al., 2011).

Selenium compounds are transported in the blood to various organs by albumin and other proteins containing sulphydryl groups, such as low-density lipoproteins, selenoprotein P and glutathione peroxidase (IARC, 1975; Schrauzer, 2000; Thiry et al., 2012).

Radioactively marked selenite or selenomethionine given orally to rats for 4 weeks were both found to be distributed to all tissues analysed, with the highest proportion in the muscles and liver (Beilstein and Whanger, 1988). Erythrocytes, spleen, lung and muscles exhibited an increased glutathione peroxidase activity, demonstrating that selenium was distributed to these tissues and used to synthesize this enzyme. Liver, kidney and heart were the organs containing the highest selenium concentrations after exposure of sheep and swine to high concentrations via ingestion and intravenous injection (Blodgett and Bevill, 1987).

8.3 Metabolism

Selenium is metabolized mainly to the intermediate selenide before entering other metabolism routes. Selenate, selenite and selenocysteine directly follow reduction reaction pathways to form selenide, whereas selenomethionine is either incorporated non-specifically into methionine-containing proteins or converted by the enzyme selenocysteine-β-lyase to elemental selenium, which can be reduced to selenide in the body (Esaki et al., 1982; Fairweather-Tate et al., 2010; Wastney et al., 2011). When selenium is present at high concentrations, selenide is methylated and excreted, but when it is present at low or normal levels, it is used in selenoprotein synthesis via incorporation into the amino acid cysteine (Suzuki, 2005; Suzuki et al., 2005; Gromadzińska et al., 2008; Wastney et al., 2011).

Organic selenium induces higher concentrations of selenium in serum and liver compared with inorganic selenium at equivalent doses, as well as a higher response in blood glutathione peroxidase activity, supportive of its higher incorporation into selenoproteins (Kim and Mahan, 2001; Wastney et al., 2011).

In a trial in which selenium was administered to 120 Chinese volunteers at amounts up to 75 µg/day for 20 weeks, both organic (selenomethionine) and inorganic selenium (selenite) increased glutathione peroxidase activity and blood selenium concentrations. The organic form induced maximal enzyme activity at a lower dose (37 µg/day) than did selenite (66 µg/day) (Xia et al., 2005). Another trial in which 90 µg selenite or 100 µg selenomethionine was administered to human volunteers for 17 weeks in New Zealand showed similar results (Thomson et al., 1982). In animals, similar results were obtained in six female rhesus monkeys exposed to selenite in the diet at concentrations of 0.25–0.5 µg/mL for 11 months (Butler et al., 1990).

At high doses (higher than suggested nutritional requirements), selenomethionine and methylselenocysteine are metabolized by methioninase and β-lyases, respectively. These pathways generate methylselenol, which can react with glutathione, as selenite does (Zhang and Spallholz, 2011). Methylselenol is believed to be the cornerstone of the anticarcinogenicity mode of action for selenium (Sanmartin et al., 2008). It can be oxidized to methylseleninic acid.

8.4 Excretion

The kidney is the main organ of selenium excretion (Zachara et al., 2001). In experimental animals and humans, selenium is excreted mainly through the urine, followed by faeces and breath, with proportions varying with the intake (Lopez et al., 1969; Martin et al., 1988). The total intake of selenium determines the extent of methylation and demethylation, which regulate the amount excreted (Thiry et al., 2012). Oral or intravenous doses of selenite given to healthy men both resulted in high urinary and, to a lesser extent, faecal excretion (Martin et al., 1988). At low and normal levels, monomethylselenium and selenosugars represent the major excretion compounds in the urine, whereas the amount of the exhaled

trimethylselenium compound increases with dose (ATSDR, 2003; Francesconi and Pannier, 2004; U.S. EPA, 2010).

Selenite has a shorter half-life in the body in comparison with selenomethionine (Patterson and Levander, 1997), because selenomethionine is an amino acid, which is recycled by the body (Swanson et al., 1991; Wastney et al., 2011). The half-life in the body is 252 days for selenomethionine and 102 days for selenite (Schrauzer, 2000).

Mice injected with 2.25 µg selenite excreted the excess selenium in faeces and urine mainly in the chemical form of 1β-methylselenol-*N*-acetyl-D-galactosamine (selenosugar) (Suzuki et al., 2010). The selenosugar was the main compound excreted in urine when rats were given water containing selenite at concentrations up to 1 µg/mL *ad libitum* for 7 days, whereas the excretion of monomethylselenium and trimethylselenium increased at selenite concentrations above 2 µg/mL (Suzuki, 2005; Suzuki et al., 2005; Thiry et al., 2012). Rats exposed to high doses of selenite excrete trimethylselenium in the urine and faeces and exhale dimethylselenide in the breath (Suzuki, 2005; Zhang and Spallholz, 2011).

The methylation of selenide generates dimethylselenide or trimethylselenium, which are excreted; this is considered to be a detoxification process (Gailer et al., 2002). When selenite was given orally to humans at a dose considered to be within the normal range (81.7 µg), trimethylselenium accounted for only 2.2% of total selenium in the urine (other metabolites were not detailed by the authors) (Martin et al., 1988). In another study, 300 µg selenite was administered orally to one man. Dimethylselenide was the only selenium compound exhaled, and its concentration spiked 1.5 hours after administration. After 10 days, the exhalation route accounted for 11% of total excretion, whereas urine accounted for 18%. Another maximum peak in blood selenium concentration was observed after 20 hours, suggestive of the existence of another, slower pathway (Kremer et al., 2005).

9.0 Health effects

9.1 Effects in humans

9.1.1 Essentiality

Selenium is considered to be an essential element by Health Canada, the Institute of Medicine (Otten et al., 2006) and other international agencies (Expert Group on Vitamins and Minerals, 2002; National Institutes of Health, 2011; WHO, 2011). It plays an important role in antioxidant defences, the immune response and the regulation of thyroid hormones by being an integral part of various selenoproteins (Zeng et al., 2009; Rayman, 2012). These selenoproteins participate directly in deoxyribonucleic acid (DNA) transcription, protein synthesis and maturation, calcium flux and oxidant scavenging (Forceville, 2006). Plasma selenium concentrations of 70–90 µg/L are considered adequate for enzyme function (Institute of Medicine, 2000).

The Institute of Medicine established a Recommended Dietary Allowance (RDA) for selenium for adolescents and adults (14–70 years of age) in Canada and the United States of 55 µg/day (Otten et al., 2006). This amount is based on two human intervention studies (Chinese male population deficient in selenium supplemented with 10–90 µg selenomethionine for 8 months, and a New Zealand population with low selenium intake given selenomethionine for 20 weeks), which demonstrated the amount needed to maximize glutathione peroxidase activity (Institute of Medicine, 2000). The average dose of selenium required to reach a plateau in glutathione peroxidase activity in both studies corresponded to 45 µg/day (including a weight adjustment for North American adults). This value is converted to the RDA of 55 µg selenium

per day[1] for people 14 years of age and over. The enzyme activity was chosen as the endpoint because a deficient activity was observed in a Keshan disease–endemic area in relation to low selenium intake.

For young people (1–18 years old), the RDA values increase progressively from 17 to 55 µg/day. For infants (0–12 months old), the RDA value is 15–20 µg/day, and for pregnant and lactating woman, it is 59–70 µg/day (Institute of Medicine, 2000).

Selenium deficiency is not expected in Canada, as food is the main source of intake, and the Canadian TDS (Health Canada, 2011) shows that the population is meeting the RDAs established by the Institute of Medicine. Natural health products (i.e., via supplementation with selenium) can also contribute significantly to the daily intake.

9.1.2 Deficiency

Selenium deficiency leads to decreased glutathione peroxidase activity, resulting in increased risk of inflammation and atherosclerotic diseases and possibly leading to an increase in the occurrence of chronic diseases (Turner and Finch, 1991; Blankenberg et al., 2003; Kohrle and Gartner, 2009).

At an average intake level of 10 µg/day, selenium is suspected to cause Keshan disease, which is characterized by cardiomyopathy (Yang, 1984), and Kashin-Beck disease, which is characterized by rheumatism. Selenium is also associated with a form of cretinism related to hypothyroidism (Spallholz, 2001; WHO and FAO, 2004; Xia et al., 2005). Keshan disease incidence was lowered and prevented by the administration of selenium in the diet in areas with very low intake of selenium in China (Yang, 1984; Cheng and Qian, 1990; Patterson and Levander, 1997). However, viruses and other nutrient deficiencies are thought to act as contributing factors together with selenium deficiency in causing these diseases (Burk, 2002; Rayman, 2008).

Selenium intake lower than 10 µg/day can lead to muscle weakness, myalgia and heart failure in some infants (WHO and FAO, 2004).

9.1.3 Acute toxicity

The most common manifestations of acute selenium toxicity are vomiting, muscle cramps, fatigue and diarrhoea. Acute selenium toxicity can also be life threatening when the following symptoms occur: pulmonary oedema, comatose state, digestive tract disturbances, heart irregularities, and renal and liver dysfunction.

Some human acute intoxications related to selenium exposure involve accidental or suicidal ingestion of products containing selenium, such as metal gun bluing agent (metal polisher). The main toxic agent in metal polishers, which consist of 2–9% selenic acid (or selenium acid) and 2–4% copper in an acid solution, is believed to be selenium. However, the product is corrosive and has a pH of 1; hence, gastric burns, among other effects, are expected.

Classical case studies are reported in Nuttall (2006), and four of these are described below.

Another complete recovery was observed after a 56-year-old man (weight not mentioned in the report) ingested 1.7 g of selenite. He vomited 1 hour after the ingestion and was admitted to hospital 4 hours later. He complained of abdominal pain, his oropharyngeal mucosa was

[1] The RDA is defined by the Institute of Medicine as equal to the value of 45 µg/day, known as the estimated average requirement, plus twice the coefficient of variation of 10% to cover the needs of 97–98% of the individuals in the group, and rounding to the nearest 5 µg.

erythematous, and electrocardiography showed a T-wave flattening. Most symptoms resolved after 2 weeks (Gasmi et al., 1997).

A 15-year-old girl (weighing 52.5 kg) ingested 400 mL of a concentrated sheep drench (vermifuge) containing selenate at a concentration of 5 mg/mL, corresponding to a dose of 22.3 mg/kg bw. She vomited 20 minutes after the ingestion and was sent to the hospital, where she was treated and recovered. Abnormal electrocardiogram (T-wave flattening) peaked at day 3 and gradually disappeared after 2 weeks. Levels of the liver enzymes aspartate aminotransferase, bilirubin and alkaline phosphatase were disturbed, but were found to be mostly normal after 1 week. The serum selenium concentration was 3100 µg/L on admission, 2100 µg/L on day 3 and 480 µg/L on day 4. The girl recovered without sequelae (Civil and McDonald, 1978).

A 40-year-old woman (weight not mentioned in the report) ingested more than 90 mL of gun bluing agent (4% selenic acid, 2.5% cupric sulphate in hydrochloric acid). She vomited and exhibited stomach haemorrhage, pulmonary oedema and kidney congestion. Death by heart failure occurred 8 hours after the incident, and her postmortem blood selenium concentration was 2600 µg/L. Tissue levels of selenium were 9–90 times those of a normal patient, whereas tissue levels of copper were about 2 times those of a normal patient. The highest levels of selenium were found in the lung (12.7 µg/g wet weight, compared with 0.15 µg/g in a normal patient) and the kidney (14.2 µg/g wet weight, compared with 1.09 µg/g in a normal patient) (Matoba et al., 1986).

The ingestion of 15 mL of a gun bluing agent by a 2-year-old boy (weight not mentioned in the report) caused multiple vomiting and diarrhoeal episodes. Initial toxic manifestations lasted for a few days and were associated with a plasma selenium concentration of 285 µg/L. Symptoms included a comatose state, digestive tract burns, heart irregularities, renal and liver dysfunction and metabolic acidosis. The boy eventually developed respiratory complications and died (Nantel et al., 1985).

Moderate intoxication has been associated with blood selenium concentrations of 1500–3100 µg/L (Civil and McDonald, 1978; Lombeck et al., 1987), whereas transient gastrointestinal disturbances occur at blood selenium concentrations of 410–930 µg/L. Ingestion of high doses of selenium contained in marketed products can be fatal; however, recovery has also been seen. Fatalities are related to the quantity ingested and blood selenium levels (Civil and McDonald, 1978; Lombeck et al., 1987; Gasmi et al., 1997; Kise et al., 2004). Postmortem blood concentrations in fatal cases have been shown to be higher than 2600 µg/L (Koppel et al., 1986; Schellmann et al., 1986).

9.1.4 Case studies: intoxication with supplements

Symptoms similar to those of long-term selenosis (hair and fingernail loss, garlic odour of the breath, gastrointestinal disturbances, irritability and fatigue) can occur following the self-administration of selenium tablets as supplements.

Inorganic selenite at a median dose of 41 mg/day from a natural health product was consumed by 210 Americans for about 2–4 weeks. One subject was hospitalized, and the majority had typical selenosis symptoms (e.g., nail abnormalities, hair loss, garlic breath, gastrointestinal disturbances) (MacFarquhar et al., 2010).

A study was performed with an intention-to-treat analysis in severe septic shock patients with an infection. Patients were injected with selenite (4000 µg on the first day, 1000 µg on each of 9 subsequent days) using continuous intravenous infusion for 10 days. No adverse events related to selenite were recorded (Forceville et al., 2007). The rationale behind the treatment relates to the fact that a drop in serum selenium level has been reported in critically ill patients and those with severe septic shock (Geoghegan et al., 2006). This could be associated with a

decrease in antioxidant defences, which would be counteracted by the injection. In contrast, the pro-oxidative effect of selenium could also inhibit the binding of NF-κB to the DNA, reducing the inflammatory response.

A 36-year-old man (weight not reported) took two tablets hourly for a few days, then 10 tablets per day, each containing selenium at concentrations between 2500 and 5000 µg/g (R.F. Clark et al., 1996). He had diarrhoea, fatigue and paraesthesia (tingling sensations in extremities) and lost some hair during the first week and became bald after 2 weeks. His nails became discoloured thereafter. After he stopped the supplements for 2 weeks, he experienced hair regrowth, his neurological symptoms disappeared and his blood and clinical chemistry tests became normal. The serum selenium level was 8.26 µmol/L (normal 0.70–1.65 µmol/L), which is equivalent to 650 µg/L using a conversion factor of 78.74 µg/µmol.

A 55-year-old woman took approximately 24 mg of selenium (species and total intake period not specified) daily. She had diarrhoea for 6 weeks, followed by hair loss for 2 weeks. She also had muscle cramps, joint pain, fatigue and difficulty concentrating (Sutter et al., 2008).

A 57-year-old woman took tablets containing 31 mg of elemental and/or organic selenium and other vitamins and minerals daily for 70 days (FDA, 1984). After 2 months, she had brittle nails, hair and nail loss, swelling and purulent discharge of the fingertips, nausea and vomiting, a sour milk breath odour and increased fatigue. No information was provided on her recovery.

Patterson and Levander (1997) reported a case study (original study sources not mentioned) that described an attempt to prevent Kashin-Beck disease by administering 250 µg of selenite to Chinese children for 60 days, followed by 500 µg/day for another 60 days. No adverse effects were observed.

A 62-year-old male took 913 µg selenite tablets daily for 2 years and developed fragile nails and garlic breath odour (Yang et al., 1983). The symptoms disappeared after he stopped taking the tablets.

In a randomized, placebo-controlled interventional study, 88 healthy American adults ingested selenite, selenomethionine or selenium-enriched yeast at 200, 400 or 600 µg/day for 16 weeks. No adverse effects were observed (Burk et al., 2006).

Overall, symptoms similar to those of chronic exposure to selenium have been observed after high selenium intakes from supplements.

9.1.5 Chronic exposure

Chronic exposure to high selenium doses causes toxicity characterized as selenosis. Selenium has also been suggested to affect other body functions, such as glucose metabolism. However, these studies present limitations, and definitive conclusions cannot be drawn.

9.1.5.1 Selenosis

Long-term exposure to high levels of selenium in food results in selenosis, characterized by hair loss, nail anomalies or loss, skin anomalies, garlic odour of the breath, tooth decay and, more severely, disturbances of the nervous system.

The most complete database on selenosis comes from a fairly large population living in a seleniferous area located in Enshi County in China.

In 1961–1964, an outbreak of selenosis affected 49.2% of the 248 inhabitants of five highly exposed villages of Enshi County, with a daily selenium intake level averaging 4.99 mg (3.20–6.69 mg), or 94.4 µg/kg bw per day (Yang et al., 1983; Patterson and Levander, 1997). The levels of selenium intake were calculated after collecting information on the dietary habits of the subjects observed and analysis of typical cereals and vegetable samples. The selenium

concentrations in food ranged between 4.0 and 11.9 mg/kg. This high selenium intake period occurred concurrently with a famine. The affected individuals showed symptoms of selenosis, characterized by hair and fingernail loss, garlic odour of the breath and, more severely, disturbances of the nervous system (fatigue, irritability, peripheral anaesthesia, numbness in the extremities, convulsions), skin changes and gastrointestinal upset. The symptoms disappeared after the diet was modified. The levels of selenium intake were estimated based on an analysis of selenium concentrations in cereals and vegetables (organic forms of selenium), urine and whole blood. In general, the concentration of selenium in drinking water for the study population represented 2–3% of the total selenium intake. The mean concentration of selenium in 11 drinking water samples was 54 µg/L (Yang et al., 1983). Among these, four samples were from the surface water of a village with a high prevalence of selenosis and had a mean selenium concentration of 139 µg/L (117–159 µg/L). The remaining seven samples were from different sources and had an average selenium concentration of 5 µg/L. The soil in the area derived from coal had a mean selenium concentration of 300 mg/kg and is responsible for the high selenium content of the plants. Samples were collected at three periods. The selenium concentrations in 10 coal samples from the selenosis-endemic area were 291 mg/kg in 1966, 367 mg/kg in 1967 and 84 123–92 800 mg/kg in 1978. The famine that occurred at that period resulted from a drought, forcing villagers to consume more vegetables and maize and less rice and other proteinous food, which is hypothesised to have contributed to the potency of the selenium toxicity (Yang et al., 1983).

In a subsequent study in Enshi County during 1985–1986, the average daily intake of selenium, based on lifetime exposure, was categorized as low (70 µg), moderate (200 µg) or high (1300 µg) in 50–75 families (n = 349 adults) (Yang et al., 1989a). To estimate total selenium intake, a questionnaire on food habits and history of toxic manifestations was administered to the families, and selenium was measured in a wide variety of food items (cooked and raw). A regression equation was then derived based on the correlation between intake estimates and selenium concentrations in tissues (whole blood, urine, hair, fingernails and toenails). This equation allowed the estimation of selenium intakes in individuals with known blood selenium concentrations. Selenosis symptoms were classified as + or ++ based on severity (++ being more severe than +) of fingernail and skin changes and hair loss (Yang et al., 1989b). The prevalence and severity of symptoms were not related to blood selenium concentration in a dose–response fashion, showing interindividual variability. These symptoms were not present in individuals with a blood selenium concentration of 1000 µg/L or below. Subjects with blood selenium concentrations in the range of 1000–2000 µg/L displayed selenosis symptoms with a severity of ++ (3–7%) and + (10–35%). Forty-five percent of individuals with blood selenium concentrations of 2000–3300 µg/L or higher displayed selenosis symptoms with a severity of + only (none were reported to have selenosis symptoms with a severity of ++). Symptoms were mostly (97% of the time) present in individuals older than 18 years, and no symptoms were present in individuals under 12 years of age. Prolonged prothrombin time was observed in 45% of individuals with a blood selenium concentration above 1000 µg/L. Persistent selenosis symptoms were observed in five Chinese individuals with blood selenium concentrations ranging between 1054 and 1854 µg/L. The authors calculated that a blood selenium concentration of 1054 µg/L corresponded to an intake of 910 µg/day and identified these as the minimum blood selenium concentration and minimum selenium intake causing toxicity, respectively.

Those same five patients were chosen for a follow-up assessment in 1992 because they had the lowest intake level showing clear signs of selenosis and their symptoms were persistent (Yang and Zhou, 1994). Between 1986 and 1992, part of their diet and corn consumption were replaced by imported grains (rice and market cereals) with a lower selenium content. By 1992,

their symptoms had disappeared, and their blood selenium concentrations had dropped from an average of 1346 µg/L to 968 µg/L, the latter representing a mean intake of 819 µg/day. The authors set the no-observed-adverse-effect level (NOAEL) at 819 µg/day. This value was rounded to 800 µg/day by the Institute of Medicine to derive the tolerable upper intake level (UL). The details provided on the selenium intake in relation to selenosis symptoms in the Yang et al. (1989a,b) study and the follow-up study of five recovered sensitive individuals (Yang and Zhou, 1994) are sufficient to allow a risk assessment for selenium to be performed.

Some possible limitations to the findings of the Yang and co-workers studies (Yang et al., 1989a,b; Yang and Zhou, 1994) were identified. For example, the health measurements of these observational studies were not exhaustive. No information was provided on the impact of the famine and the low protein content diet on the health effects of selenium in the population. Moreover, although the cohort was exposed to relatively high levels of selenium in drinking water, the main source of exposure was through the diet, in which selenium in the organic form selenomethionine is predominant. The burning of coal for cooking could have contributed to the selenium intake via inhalation, but no quantitative information was provided.

Although these potential biases could have influenced the quantification of the exposure, the selenium toxicity data from these studies on a relatively high number of subjects (n = approximately 400) are useful in the analysis of the dose-response. The use of this study is also supported by the relevance and the causality of selenium intake with the adverse health outcomes. The correlation between selenium content in food measured in multiple items consumed by the subjects with levels of selenium in various tissues allows a quantitative estimation of the intake and identification and use of a NOAEL in the risk assessment of selenium.

Other studies, supporting the findings of the studies by Yang and co-workers (Yang et al., 1989a,b; Yang and Zhou, 1994), are described below.

Over a 2-year period, 142 subjects of both sexes from South Dakota and eastern Wyoming, another area with high levels of selenium, were randomly recruited to participate in a clinical examination survey (Longnecker et al., 1991). This population consumed grains with high selenium concentrations (average 239 µg/day, highest intake 724 µg/day). Concentrations of selenium in blood, serum, urine and nails was correlated with the intake levels. A duplicate-plate food and beverage collection for selenium analysis was also performed. Higher selenium concentrations in whole blood and nails were associated with a decrease in symptoms such as paraesthesia and an increase in lethargy. Selenium intake also correlated with aminotransferase concentrations in the serum. As physical injury in ranchers could influence physiological parameters, the authors included an indicator variable (rancher or not) to assure that individuals were randomly selected. After correction for rancher status, the evidence for selenosis was no longer significant. Despite a lack of details on statistical analysis and study protocol provided by the authors, the doses reported to be associated with no selenosis symptoms are supportive of the results of the studies by Yang and co-workers (Yang et al., 1989a,b; Yang and Zhou, 1994).

No evidence of selenosis was observed in a cross-sectional study involving 448 individuals aged 15–87 years living in the Amazon (Tapajos River basin, Brazil) with a diet high in selenium (Lemire et al., 2012). Blood selenium concentrations ranged between 103 and 1500 µg/L. Because the population was also exposed to mercury, the authors suggested that this co-exposure might be protective of selenosis.

In a survey that compared the health status of 111 children from a rural, seleniferous zone in Venezuela with that of 50 urban children from the city of Caracas (Jaffe et al., 1972), the rural children showed a higher concentration of selenium in blood (813 µg/L versus 355 µg/L) and urine (636 µg/L versus 224 µg/L). Although some selenosis symptoms were present in children

from the rural zone (dermatitis and nail anomalies), the authors concluded that there was no clear sign of toxicity that could be attributable to selenium because of the presence of multiple differences between the two subpopulations.

No evidence of selenosis was observed in Inuits of Greenland (n = 222 subjects of both sexes) (Hansen et al., 2004). Mean whole blood selenium concentrations were in the range of 80–1890 µg/L, and whale skin was found to be the main source of intake, with a selenium concentration of 47.9 µg/g.

In conclusion, selenosis effects were observed and characterized in a Chinese population having high intakes of selenium from food (Yang et al., 1989a,b; Yang and Zhou, 1994). No selenosis symptoms were observed in subpopulations of children in the studies from China, Venezuela, Greenland or the Amazon.

9.1.5.2 Effects on cancer

Selenium is not considered to be a carcinogen, and multiple studies have focused on its anticarcinogenic potential (Hurst et al., 2012; Rayman, 2012).

A Cochrane Systematic Review of several observational studies and randomized controlled trials suggested a protective effect of selenium against cancer (Dennert et al., 2011). The meta-analysis of 13 prospective observational studies showed a reduction in cancer incidence (odds ratio [OR] = 0.69, 95% CI = 0.53–0.91) and in cancer mortality (OR = 0.55, 95% CI = 0.36–0.83) in both sexes. The organs with the greatest reduction in cancer risk were the bladder (OR = 0.67, 95% CI = 0.46–0.97), lung (OR = 0.75, 95% CI = 0.54–1.03) and prostate (OR = 0.78, 95% CI = 0.66–0.92). The pooled results from the observational studies were suggestive of a slight protective effect for cancer incidence in individuals with a higher selenium status (blood, nail and hair biomarkers of exposure) compared with those with a lower status (OR = 0.69, 95% CI = 0.53–0.91). The authors stated that it is difficult to conclude on the validity of this tendency because of the heterogeneity of the data. The review also included an analysis of six randomized clinical trials focusing on prostate cancer, non-melanoma skin cancer and liver cancer, among them the Nutritional Prevention of Cancer (NPC) and the Selenium and Vitamin E Cancer Prevention Trial (SELECT), the two largest trials using selenium-only supplementation. Of the six randomized clinical trials, two were conducted with selenium-enriched yeast for the prevention of non-melanoma skin cancer, one with selenomethionine for the prevention of prostate cancer and three with selenium-enriched yeast or selenite for the prevention of liver cancer. A protection against all-cancer, colorectal, lung and prostate cancer mortality and prostate cancer incidence was observed in the NPC and in the observational study, the Third National Health and Nutrition Examination Survey (NHANES III), respectively. After a mean follow-up of 7.4 years, the subjects receiving selenium supplements in the NPC study had an increase in non-melanoma skin cancer (relative risk [RR] = 1.17, 95% CI = 1.02–1.34) and squamous cell carcinoma (RR = 1.25, 95% CI = 1.03–1.51). The increase in squamous cell carcinoma incidence was also observed in the subjects in the highest tertiles (105.6–122.0 ng/mL and > 122.4 ng/mL) (RR = 1.49, 95% CI = 1.05–2.12; and RR = 1.59, 95% CI = 1.11–2.30). However, these results should be interpreted cautiously, as described below. The increase in non-melanoma skin cancer incidence was mainly observed in a subgroup, located in one cancer centre (Macon, Georgia), receiving 200 µg of selenomethionine per day of the trial (Duffield-Lillico et al., 2003; Reid et al., 2008). The subjects consisted of patients with skin cancer history and skin that had sustained heavy sun damage (Duffield-Lillico et al., 2003; Reid et al., 2008). No dose–response relationship for non-melanoma skin cancer or squamous cell carcinoma risk was observed in relation to the administered dose: the group receiving 400 µg selenomethionine per day had no significant difference in cancer risk, with hazard ratios (HR) of 0.91 (95% CI =

0.69–1.20) and 1.05 (95% CI = 0.72–1.53), respectively. After correction for cases that occurred at the beginning of the trial, no significant increase in squamous cell carcinoma risk was seen (HR not given by the author) (Dennert et al., 2011). The reasons for the different effects observed between doses and trial locations remain unclear and were suspected to be related to chance, as distribution of factors was similar between sites (Dennert et al., 2011).

A meta-analysis of 12 studies (9 on plasma/serum selenium, 3 on toenail selenium; total *n* = 13 254 individuals) looked at the relationship between prostate cancer risk and selenium biomarkers (Hurst et al., 2012). Randomized controlled trials, case–control studies and prospective cohort studies were included in the analysis. Increasing plasma/serum selenium concentration (up to 170 ng/mL) was related to a decrease in prostate cancer risk. Similarly, toenail selenium concentrations between 0.85 and 0.94 µg/g indicated a reduction in prostate cancer risk (estimated RR = 0.29; 95% CI = 0.14–0.61). However, toenail concentrations higher than 0.94 µg/g seemed to increase cancer risk, but the authors gave no details or comments on the tendency.

The NPC trial is a randomized, double-blind clinical trial that was designed to address skin cancer incidence following supplementation with selenium-enriched yeast (consisting mostly of selenomethionine) at 200 µg selenomethionine per day for a mean of 4.5 years between 1983 and 1991 (L.C. Clark et al., 1996, 1998). The population consisted of 1312 American male patients with skin cancer history (Duffield-Lillico et al., 2003). No skin cancer protection was observed, but significant reductions in total (HR = 0.75, 95% CI = 0.58–0.97) and prostate cancer incidence (HR = 0.48, 95% CI = 0.28–0.80) were observed compared with placebo. In a 2002 follow-up study, results were presented from 1991 through 1996 (Duffield-Lillico et al., 2002). They confirmed the cancer protection trend for total and prostate cancer incidence. However, lung (HR = 0.74, 95% CI = 0.44–1.24) and colorectal (HR = 0.46, 95% CI = 0.21–1.02) cancer incidences were no longer significantly reduced. The decrease in prostate cancer incidence was statistically significant in men with initially low baseline serum levels of selenium (< 121.2 ng/mL) and prostate-specific antigen levels (< 4 ng/mL) (Clark et al., 1998). The cancer protection observed in the NPC trial is restricted to men with plasma selenium concentrations lower than 121.6 µg/L (Duffield-Lillico et al., 2002).

SELECT is a phase III randomized, double-blind trial including 35 533 men older than 50 years without clinical evidence of prostate cancer from the United States (including Puerto Rico) and Canada (Klein et al., 2003). Selenium (200 µg selenomethionine per day) was administered as a supplement. The men, who had prostate-specific antigen levels below 4 ng/mL at baseline, were followed for 7–12 years with normal digital rectal exams. No lower prostate cancer (HR = 1.04, 95% CI 0.90–1.18) incidences were observed with selenium supplementation compared with the placebo group (Klein, 2009; Lippman et al., 2009). Also, there were no increases in secondary outcome cardiovascular events or mortality risk measurements. However, the trial was stopped early because of statistically non-significant increased risks of prostate cancer in the vitamin E group and of type II diabetes mellitus in the selenium group (RR = 1.07, 99% CI = 0.94–1.22).

NHANES III (1988–1994) was a large longitudinal epidemiological study using a multistage probability cluster designed to compile physical conditions involving a representative sample of the U.S. population (16 573 adults). The mean serum selenium concentration was 125.6 µg/L in 13 887 individuals (Bleys et al., 2008). Concentrations up to 130 µg/L were inversely correlated to all-cause, all-cancer and colorectal, lung and prostate cancer mortality HR, when comparing the tertiles (< 117 µg/L, 117–130 µg/L and > 130 µg/L) of serum selenium concentration by Cox proportional hazards regression. When serum selenium concentration

exceeded 130 µg/L, all-cancer and all-cause mortality had a non-significant increase. However, no causality relationship can be drawn based on observational studies.

One study on 2065 residents of Reggio Emilia, Italy, focused on mortality during a 12-year period following a relatively high intake of selenate in the drinking water (7–9 µg/L) (Vinceti et al., 2000). The authors found a slight increase in mortality from neoplasms in people exposed to high levels of selenate (standardized mortality ratio [SMR] = 1.17, 95% CI = 0.96–1.42) compared with the rest of the municipality, who were exposed to an average concentration of selenate in drinking water of 1 µg/L. However, this study had several limitations, such as the lack of statistical analysis, physiological selenium status and adjustments based on lifestyle, smoking and alcohol consumption. In addition, the level of exposure and the characteristics of the control population were not defined. Consequently, no valid conclusions can be drawn from this study.

Other epidemiological studies found an inverse association of selenium with cancer. A lung cancer study in Maryland found an inverse, but non-significant ($P = 0.08$), association ($r = -0.58$) between serum selenium concentrations from 25 802 people and risk of lung cancer (OR not provided by the authors) (Comstock et al., 1997). Among another cohort of 10 940 people from the United States, 111 cancer patients were matched to 210 cancer-free controls based on age, sex, race, smoking history and general health status and followed for 5 years (Willett et al., 1983). Selenium concentrations in the serum ($\log_e$ transformed) were found to be lower in cancer patients (0.129 ± 0.002 µg/mL [standard error of the mean (SEM)]) than in the controls (0.136 ± 0.002 µg/mL [SEM]) (paired *t*-tests, $P = 0.02$ for total cancer association with selenium levels). The gastrointestinal cancers had the strongest inverse association with selenium concentrations (cases: 0.114 µg/mL; controls: 0.134 µg/mL; $P = 0.01$).

The European Prospective Investigation into Cancer and Nutrition (EPIC) investigated the relationship between environmental factors and health outcome in 520 000 people in 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom (Allen et al., 2008). Analysis of the data from 959 patients that had prostate cancer at the time of blood sampling and 1059 matched controls with a median age of 60 years was conducted. The geometric mean plasma selenium concentrations were 71.9 µg/L and 70.6 µg/L for the cancer cases and controls, respectively. When comparing the highest quintile (> 84 µg/L) with the lowest quintile (< 62 µg/L) of plasma selenium concentration, no correlation with prostate cancer risk was found (RR = 0.96, 95% CI = 0.70–1.31), with or without adjustment for smoking, alcohol and other factors, independently of the stage of illness.

In conclusion, the human epidemiological studies on selenium and cancer are inconsistent. There is no clear indication that high selenium exposure causes a decrease or an increase in the risk of cancer, and thus no clear indication that there is any effect at all, as concluded by the World Health Organization and the Food and Agriculture Organization of the United Nations in 2004 (WHO and FAO, 2004). Inverse associations between selenium status and cancer risk have been reported in observational studies (Fairweather-Tait et al., 2011; Rayman, 2012); however, trial findings have been mixed. Beneficial effects on cancer are observed in trials in which selenium blood concentrations were relatively low before the selenium supplementation had started (Boosalis, 2008; Rayman, 2012).

9.1.5.3 Cardiovascular effects

Epidemiological evidence for the relationship between selenium and cardiovascular disease is contradictory. Observational studies have generally reported an inverse relationship between selenium status and cardiovascular disease, in particular in populations with low levels of intake (Flores-Mateo et al., 2006; Rayman et al., 2011). In contrast, more recent studies have

suggested a U-shaped dose–response relationship, with potential harm occurring at selenium levels both below and above a physiologically adequate range (Stranges et al., 2010; Rees et al., 2012).

In a meta-analysis performed by Flores-Mateo et al. (2006), results from 25 observational (14 prospective cohort and 11 case–control) and 6 randomized studies published between 1982 and 2005 were pooled separately to assess the relationship between selenium biomarkers and cardiovascular health and the efficacy of supplementation in preventing coronary heart disease, respectively. In the randomized clinical studies, a non-significant reduction (RR = 0.89, 95% CI = 0.68–1.17) in risk of coronary events was observed with selenium supplementation; however, the authors concluded that the trials were small, and other nutrient supplements were taken in addition to selenium in most studies, resulting in inconclusive results. The NPC trial was one of them. No increase in risk of all cardiovascular disease was observed after supplementation with 200 µg selenomethionine per day in this study after the entire 7.6 years of follow-up (HR = 1.03, 95% CI = 0.78–1.37) (Stranges et al., 2006). In contrast, a moderate inverse association was seen in the observational studies. Based on the blood or serum selenium status, a 50% increase in selenium was associated with a significant decrease (24%) in the risk of cardiovascular disease (RR = 0.76, 95% CI = 0.62–0.93); however, the authors questioned the validity of this result, because previous observational studies with other antioxidants and vitamins were unreliable and not supported by clinical trials on their efficacy in a relationship with cardiovascular disease prevention.

In more recent cross-sectional studies and longitudinal observational studies, mixed results have been observed, suggesting a non-linear dose–response relationship between selenium and cardiovascular disease (Bleys et al., 2008). Increasing selenium levels in the body were associated with potential protection against cardiovascular disease up to a concentration of 130–150 µg/L in the mortality follow-up study of NHANES III (Bleys et al., 2008), whereas adverse cardiovascular-related effects were observed in cross-sectional analyses of populations with high selenium status, such as those in the United States (Laclaustra et al., 2009, 2010). These data come from serum selenium measurements from 13 887 U.S. adults of both sexes who participated in NHANES III.

However, results from cross-sectional studies should be interpreted with caution, because of the possibility of reverse causation and potential confounding effects by unmeasured or unknown factors. In addition, it should be noted that recent findings from a clinical trial in the United Kingdom (i.e., the UK-PRECISE trial) suggest potential beneficial effects of selenium supplements on blood lipids in a group of elderly volunteers with relatively low selenium status (Rayman et al., 2011). The applicability of these findings to other populations is uncertain.

Furthermore, in *post hoc* analyses from the NPC trial, selenium supplementation (200 µg/day as high-selenium yeast) was not significantly associated with any of the cardiovascular disease endpoints after 7.6 years of follow-up (HR= 1.03, 95% CI = 0.78–1.37) (Stranges et al., 2006).

In a prospective study among 636 individuals suspected to have coronary heart disease, the patients with the highest level of activity of red blood cell glutathione peroxidase had an HR of 0.27 (95% CI = 0.15–0.58; $P < 0.001$), compared with those with the lowest activity, suggesting a beneficial effect of selenium (Blankenberg et al., 2003).

There is no clear mode of action defining the effects of selenium on the cardiovascular system, and additional studies will need to be conducted to examine the relationship between selenium and cardiovascular disease across a wider range of selenium concentration (Stranges et al., 2010; Rayman et al., 2011).

In conclusion, the results of epidemiological studies and clinical trials on the effects of selenium on cardiovascular disease are mixed and do not suggest a protective effect of selenium on cardiovascular disease at this time (Stranges et al., 2010; Rees et al., 2012). Findings from NPC, SELECT and UK-PRECISE were based on *post hoc* analyses of the main trial, raising concerns about the robustness of results from secondary endpoints or subgroup analyses of clinical trials (Freemantle, 2001; Brookes et al., 2004).

9.1.5.4 Relationship with diabetes

Several studies have investigated the relationship between selenium and diabetes and have shown mixed results.

Many observational studies have found protective effects in terms of diabetes or dysglycaemia incidence in individuals with relatively high selenium status (Navarro-Alarcón et al., 1999; Stapleton, 2000; Kljai and Runje, 2001; Rajpathak et al., 2005; Bleys et al., 2007; Kornhauser et al., 2008; Akbaraly et al., 2010). For example, a recent pooled longitudinal analysis from two U.S. cohorts showed inverse associations between toenail selenium levels and incident type II diabetes, with a reduced diabetes risk across quintiles of toenail selenium (*P* for trend = 0.01) (Park et al., 2012). However, other observational and interventional studies, such as the secondary analysis of the Supplementation with Antioxidant Vitamins and Minerals (SU.VI.MAX) trial, found an increased risk of type II diabetes incidence or prevalence among subjects with higher selenium status (Czernichow et al., 2006; Bleys et al., 2007; Laclaustra et al., 2009).

Laclaustra et al. (2009) used NHANES III data from 917 adults aged 40 or older to determine the association between serum selenium levels and diabetes. Diabetes was defined as a self-report of current use of medication or a fasting plasma glucose greater than 126 mg/dL. The mean serum selenium level was 137.1 µg/L. The study found that the odds of having diabetes was significantly higher for the participants in the highest quartile of serum selenium (>147 µg/L) compared with the ones in lowest quartile (<124 µg/L) (OR = 7.64, 95% CI = 3.3-17.5). However, no definitive conclusions on causality can be drawn since the study has several limitations, as follows: (1) the cross-sectional design of the NHANES does not allow temporality in the association (i.e., if the high selenium levels are the cause or a consequence of the association with diabetes); (2) the single measurement of serum selenium levels as a biomarker of exposure reflects short-term intake and may be subject to within-person variability; and (3) the trend for diabetes and cardiovascular diseases risk are non-linear (no dose-response).

Two secondary analyses of randomized clinical trials, which have kept the original randomization design, have observed some positive associations between selenium levels and diabetes incidence. However, it is difficult to draw conclusions from these results, because the trials were not designed specifically to evaluate the effects of selenium on diabetes. The SELECT study (described in section 9.1.5.2) observed a non-significant increased risk of type II diabetes (RR = 1.07, 95% CI = 0.94–1.22, *P* = 0.16) after selenomethionine was administered at 200 µg/day to 35 533 men followed for 7–12 years (Klein, 2009; Lippman et al., 2009). In the NPC trial (described in section 9.1.5.2), however, the observed increase in type II diabetes cases was significant (HR = 1.55, 95% CI = 1.03–2.33, *P* = 0.03). Moreover, based on plasma selenium levels, a significant dose-related increase in risk (*P* = 0.038) was observed across the tertiles of plasma selenium baseline concentration (HR = 2.70, 95% CI = 1.30–5.61, in the highest tertile, > 121.6 µg/L) (Stranges et al., 2007).

In both NPC and SELECT, diagnosis of type II diabetes was based on self-report or use of diabetes medication rather than on biomarker data. This may have led to some misclassification (under-diagnosis) of diabetes at baseline or during the trials. However, given

the randomized design and blinding, differential misclassification according to treatment assignment is unlikely. The results cannot readily be generalized to the general public because of the selective nature of the participants randomized in these trials. The NPC trial sample consisted of elderly individuals (mean age 63.2 years) with a history of skin cancer from the eastern United States. Finally, the UK-PRECISE trial sample was based on a group of relatively healthy elderly, mostly white, volunteers, aged 60–74 years, recruited from four general practices in different parts of the United Kingdom.

The conclusions drawn from the results of randomized clinical trials on secondary endpoints such as diabetes are not appropriate for the risk assessment of selenium in drinking water. Their weaknesses include the fact that they were designed to assess the anticarcinogenicity effects of one dose of selenium supplements, which does not allow the establishment of a safe level of exposure to an environmental contaminant. Also, the post-analysis association with secondary endpoints is liable to result from confounders and improper design. Overall, the results are mixed, and no definitive conclusion can currently be drawn on the relationship between selenium intake and the onset of diabetes (Stranges et al., 2010; Rees et al., 2012). However, the consistency in the results of these studies does suggest the need for additional research on this topic.

9.1.5.5 Relationship with other diseases

A number of other diseases, such as amyotrophic lateral sclerosis (ALS) (Vinceti et al., 2010) and glaucoma (Bruhn et al., 2009), have shown a potential association with selenium, but the evidence is insufficient to draw conclusions due to methodological issues.

In a population-based case–control study in Reggio Emilia, Italy, a relationship between selenium and ALS was observed (Vinceti et al., 2010). After adjusting for cofactors and other exposure factors, consumption of "drinking water with ≥ 1 µg/L Se" was associated with an increased risk of ALS (RR = 4.2, 95% CI = 1.1–16). Although the study suggests that selenium-induced ALS may occur at low levels of exposure in drinking water, the semi-qualitative and retrospective exposure projections are not appropriate to use for risk assessment. Moreover, a selection bias may have occurred, in that the subjects were sampled from a population where a cluster of ALS and selenium contamination had already been perceived by the investigators.

In a small case–control study (Bruhn et al., 2009), a significantly higher glaucoma prevalence was observed in the middle and highest tertiles (183.5–215.9 ng/mL; 218.5–398.8 ng/mL) of serum selenium concentration in comparison with the lowest tertile (127.3–182.6 ng/mL). However, no dose–response relationship was observed across tertiles of aqueous humour selenium level of the eye. The small sample size and control–case ratio (~1:1) may have hampered adequate adjustment of confounders. The authors also mentioned an internal publication of a trial at the University of Arizona in which a relationship between glaucoma prevalence and blood selenium levels was observed, but gave no further details.

Selenium is recognized as essential to the functioning of the thyroid gland (Johnson et al., 2010). The effects of selenium on thyroid metabolism were evaluated in a review of two cross-sectional studies and three interventional studies in New Zealand (Thomson et al., 2005). Correlations between plasma selenium levels and thyroid status were not significant in the cross-sectional studies. Only one interventional study demonstrated a significant decrease ($P = 0.0045$) in thyroxine in response to the administration of varying levels of selenomethionine in 52 adults divided into five groups (0, 10, 20, 30 or 40 mg). The objective of the study was to evaluate the effect of selenium supplementation on glutathione peroxidase activity, and the subjects had low levels of plasma selenium (less than 100 µg/L) (Duffield et al., 1999).

9.1.6 Developmental and reproductive toxicity

Research on the developmental and reproductive toxicity of selenium in humans is sparse, and there is no conclusive evidence demonstrating toxicity to these systems. No studies demonstrated the teratogenicity of selenium in humans (OEHHA, 2010). The Institute of Medicine (2000) indicated that there are no reports of symptoms of teratogenicity in infants born to mothers with high levels of intake of selenium (without toxicity).

In Rivalta, Italy, Vinceti et al. (2000) reported the rate of spontaneous abortions and congenital malformations among women exposed to drinking water with concentrations of selenate of 7–9 µg/L for the entire gestational period, compared with women exposed to drinking water with selenate concentrations below 1 µg/L, between 1972 and 1988. Computerized birth records (n = 1974) from the General Registry Office for all Rivalta residents were reviewed, and no adverse effects on human reproduction were observed, except for a non-significant excess rate of abortion (rate ratio = 1.73, 95% CI = 0.62–4.8).

The Western Human Nutrition Research Center of the Agricultural Research Service in California evaluated the effects of selenium on about 30 healthy men aged 18–45 years for 1 year (Hawkes and Turek, 2001). The participants were divided between a high (300 µg/day) and a low (10 µg/day) food-based selenium diet for 99 days, food selenium being replaced by selenite on days 111–117 at their respective levels. In the high-selenium group, sperm motility was decreased by 32% on week 13 and in a lower fashion (17%) on week 17 compared with baseline, or week 0. Sperm concentration and number decreased significantly by more than 50% in both groups. However, environmental and dietary factors were suggested as confounders by the authors. In a recent experiment by the same investigators, with more participants (n = 42) for a longer period (48 weeks), no difference in sperm quality was observed (Hawkes et al., 2009). No effects on thyroid hormone metabolism (blood triiodothyronine and thyroxine hormone levels), body composition (fat free and fat mass) or vascular responsiveness (arterial diameter and blood flow rate) were observed in a cohort of healthy men administered 300 µg selenium-enriched yeast per day for 3–6 weeks (Hawkes et al., 2008).

OEHHA (2010) also reported case studies on sperm quality and quantity. Generally, no correlation or a positive correlation was observed between these parameters and blood selenium concentrations. For example, in a cross-sectional study in the United States, no significant relationship was observed between selenium and the rate of birth defects in 1986 in Nebraska (42 out of 453 communities had drinking water levels higher than 0.01 mg/L). Moreover, no teratogenicity effect of high selenium exposure (subjects with mean urinary levels of 0.38 mg/L) was observed in Venezuela.

In conclusion, there is no clear evidence supporting the developmental or reproductive toxicity of selenium.

9.2 Effects on experimental animals

The effects of exposure of experimental animals to selenium are variable and have been shown to depend on many factors, such as the animal species and type (rodents versus livestock), selenium species, dose, duration and route of exposure, diet, physiological status, presence of other contaminants or nutrients and stress (Valdiglesias et al., 2009). Selenium is also considered essential to animal health (Davis et al., 1999; Nogueira and Rocha, 2011).

9.2.1 Acute toxicity

Acute exposure of laboratory animals to very high levels of selenium results in respiratory failure, liver and kidney necrosis and congestion, and a decrease in locomotor activity (Civil and McDonald, 1978; Griffiths et al., 2006). For selenite, the oral median lethal doses

(LD_{50} values) reported in the literature for mice and rats ranged between 3.2 and 50 mg/kg bw (Morss and Olcott, 1967; Pletnikova, 1970; Cummins and Kimura, 1971; Vinson and Bose, 1981; Plasterer et al., 1985; Griffiths et al., 2006). The oral LD_{50} in female guinea pigs was 2.3 mg/kg bw, and in female rabbits, 1 mg/kg bw (Pletnikova, 1970).

The form of selenium administered has an impact on its acute toxicity (Nuttall, 2006). Cummins and Kimura (1971) observed large differences in oral LD_{50} values for Sprague-Dawley rats when different forms of selenium (including oxidation states and solubility) were administered. The oral LD_{50} values were 7 mg/kg bw for selenite, 138 mg/kg bw for selenium sulphide and 6700 mg/kg bw for elemental selenium. Symptoms occurring within 18–72 hours following administration and prior to death included pilomotor activity, decreased activity, dyspnoea, diarrhoea, anorexia and cachexia (body weight loss). Blood selenium concentrations correlated well with the toxicity observed with the different forms of selenium administered.

Oral LD_{50} values have been reported in the literature for other forms of selenium: selenocysteine, 35.9 mg/kg bw (male mice); and selenium-enriched yeast, 4.07–37.3 mg/kg bw (rats and mice) (Vinson and Bose, 1981; Sayato et al., 1997). No reliable data were available for selenate administered orally.

In conclusion, acute exposure to selenium has been shown to cause respiratory failure, liver and kidney necrosis, decreased activity, dyspnoea, diarrhoea and death.

9.2.2 Short-term exposure

Short-term oral exposure of laboratory animals to selenium resulted in decreased water consumption, which was considered to be responsible for the subsequent decrease in body weight and renal papillary degeneration. Moreover, hunched posture, decreased weights of heart, spleen and thymus, centrilobular hepatocyte enlargement, hypertrophy of the zona glomerulosa cells of the adrenal glands, growth retardation and disturbances of the cardiovascular, respiratory, renal, endocrine, neurological and tegumentary (skin and hair) systems have been reported.

A study by the U.S. National Toxicology Program (NTP) (Abdo, 1994) exposed F344/N rats and B6C3F1 mice (10 of each sex per concentration) to selenate in drinking water at concentrations of 0, 3.75, 7.5, 15, 30 or 60 mg/L daily for 90 days. The concentrations were estimated to be equivalent to selenium doses of 0, 0.1, 0.2, 0.4, 0.6 and 1.1 mg/kg bw per day (males) or 0, 0.1, 0.2, 0.4, 0.6 and 0.8 mg/kg bw per day (females) for rats and 0, 0.3, 0.5, 0.8, 1.5 or 2.6 mg/kg bw per day for mice. All rats died in the 60 mg/L group (by week 11 for males and week 6 for females). Mean body weights in rats dosed with 30 mg/L and in mice dosed with 30 and 60 mg/L were reduced (13–29%) compared with control animals. Decreased water consumption was observed in rats and mice exposed to 15 mg/L and above. Administration of selenate at concentrations of 7.5 mg/L or higher was associated with increased incidences of renal papillary degeneration in rats, in which dehydration may have played a role. Dehydration was considered to be responsible for the observed decrease in urine volume and increases in erythrocyte counts, haematocrit, haemoglobin concentrations, alanine aminotransferase activities, urea nitrogen and urinary specific gravity in rats. No renal lesions were seen in mice. Blood chemistry values for treated mice were similar to those of the controls.

In the same NTP drinking water study (Abdo, 1994), F344/N rats and B6C3F1 mice (10 animals of each sex per dose group) were also exposed to selenite at concentrations of 0, 2, 4, 8, 16 or 32 mg/L daily for 13 weeks. These concentrations were estimated to be equivalent to selenium doses of 0, 0.08, 0.13, 0.2, 0.4 and 0.8 mg/kg bw per day (males) or 0, 0.08, 0.13, 0.2, 0.4 and 0.9 mg/kg bw per day (females) for rats and 0, 0.14, 0.3, 0.5, 0.9 or 1.6 mg/kg bw per day for mice. Two female rats exposed to 32 mg/L died. Mean body weights were reduced (17–

54%) in rats and mice exposed to 32 mg/L compared with controls. Water consumption was reduced in rats and mice with increasing selenite concentration. Selenite induced similar changes in haematology, clinical chemistry and urinalysis parameters in rats as did selenate. These effects may also have been induced by dehydration. Selenite also increased the incidence of renal papillary degeneration in rats at 0.8 mg/L and above. Dehydration may have contributed to the effects observed in rats and mice. Selenite did not cause lesions in mice.

Although some effects on decreased water consumption and renal papillary lesions were observed at a lower dose (7.5 mg/L), the author estimated the NOAEL in rats to be 0.4 mg/kg bw per day for selenate and selenite expressed as selenium, based on mortality, body weight depression, decreased water consumption and renal papillary lesions (Abdo, 1994). The estimated NOAEL in mice was 0.8 mg/kg bw per day for selenate expressed as selenium and 0.9 mg/kg bw per day for selenite expressed as selenium, based on body weight depression and decreased water consumption.

Sprague-Dawley rats (10–13 rats of each sex per dose group) were exposed to selenate in drinking water at 0, 7.5, 15 and 30 mg/L (estimated to be equivalent to doses of 0, 0.5, 0.8 and 1.1 mg/kg bw) for 30 days (NTP, 1996). Female rats were divided among three groups: peri-conception, gestational and vaginal cytology. Maternal and male body weights were reduced in all selenate dose groups. The groups exposed to 0.8 and 1.1 mg/kg bw demonstrated symptoms of toxicity, such as pale and small adrenals, thickened stomach walls, stomach adhesion involving abdominal organs, enlarged and small kidneys, enlarged spleen and implantation sites with nodular material. No NOAEL was determined, as reduced body weight occurred in all treated groups.

Swiss mice were exposed to selenite daily in drinking water at concentrations of 1–64 mg/L for 46 days (Jacobs and Forst, 1981b). Reduced survival and decreased body weight were observed at 64 mg/L, with females being more tolerant than males, whereas concentrations of 1, 4 and 8 mg/L enhanced survival and growth The authors did not identify a NOAEL.

The effect of a selenium-enriched yeast preparation was evaluated in Sprague-Dawley rats (both sexes) and beagle dogs (both sexes) for 28 or 90 days (Griffiths et al., 2006). Selenium in yeast is in the form of selenomethionine (98%). In the 28-day study, rats were dosed with selenium at 0, 0.1, 0.51, 2.0 or 5.1 mg/kg bw per day (n = 6 per group), and dogs were dosed with selenium at 0, 0.045, 0.225 or 1.125 mg/kg bw per day (n = 4 per group). In the 90-day study, rats were dosed with selenium at 0, 0.23, 0.36 or 0.61 mg/kg bw per day (n = 20 per group), and dogs were dosed with selenium at 0, 0.06, 0.2 or 0.6 mg/kg bw per day (n = 8 per group). Another group was also administered selenite at 0.35 mg/kg bw per day (rats) and 0.6 mg/kg bw per day (dogs) in the 90-day study. No mortality occurred as a result of treatment in the groups. In the 28-day rat study, hunched posture was observed in the 0.51 mg/kg bw per day group and higher. The two highest dose groups were terminated because hunched posture occurred on day 4 and onward. Excessive salivation was observed in dogs in the high-dose group, and decreased erythrocyte count, haemoglobin concentration and packed cell volume were observed in the 0.225 mg/kg bw per day dose groups. A reduced dietary intake for all groups of rats was observed in the 90-day study. Moreover, fur loss, hunched posture, a decrease in male rat heart, spleen and thymus organ weights, centrilobular hepatocyte enlargement and hypertrophy of the zona glomerulosa cells of the adrenal glands were observed at selenium doses above 0.23 mg/kg bw per day and in the selenite group. In the 90-day treated dog groups, an emaciated appearance and decreases in erythrocyte count, haemoglobin concentration, packed erythrocyte volume and mean cell hemoglobin concentration were observed at 0.6 mg/kg bw per day. Higher cholesterol levels were observed in the 0.2 mg/kg bw per day group. The NOAELs were 0.1 mg/kg bw per day for rats and 0.045 mg/kg bw per day for dogs in the 28-day study.

The NOAELs were 0.23 mg/kg bw per day for rats and 0.06 mg/kg bw per day for dogs in the 90-day study.

Signs of selenosis (loss of hair, lesions of hooves) were observed in livestock (calves, steer and pigs) administered selenite, selenomethionine or selenium-enriched yeast (organic) either in the diet or by gavage (selenite or selenium-enriched yeast at concentrations above 5–20 mg/kg of food for pigs and selenite and selenomethionine at concentrations of 0.28–0.8 mg/kg bw for steers and calves) in short-term studies (O'Toole and Raisbeck, 1995; Kim and Mahan, 2001; Kaur et al., 2003).

OEHHA (2010) reported on various studies relating to the health effects seen in mice and rats as a result of short-term oral exposure (14 days to 3 months) to selenite, selenate and organic compounds such as selenomethionine. Rats were the most sensitive species, and adverse effects observed at concentrations above the NOAELs of 0.026–0.50 mg/kg bw include growth retardation and disturbances of the cardiovascular, hepatic, respiratory, renal and endocrine systems. The highest NOAEL observed for these health effects was 1.67 mg/kg bw for selenite following a 13-week exposure. Organic selenium, such as selenomethionine, induced the same adverse effects at concentrations above the NOAELs of 0.125–0.320 mg/kg bw in rats. These endpoints were also observed in mice, with NOAELs in the range of 0.20–7.17 mg/kg bw. Gastrointestinal, ocular and muscular disturbances were observed at doses above 7.17 mg/kg bw in mice. Selenomethionine induced the same effects, in addition to neurological disturbances, at doses above the NOAELs in the range of 1.36–1.96 mg/kg bw in mice. Pigs, calves and monkeys exhibited the same adverse effects as rats, as well as neurological and dermal disturbances, after oral exposures to doses above the NOAELs of 0.014–1.25 mg/kg bw. Selenomethionine induced these effects at doses above 0.08–1.25 mg/kg bw.

9.2.3 Long-term exposure and carcinogenicity

Most carcinogenicity studies with selenate, selenite and organic selenium compounds have shown negative results in laboratory animals, and exposure to selenium may delay the onset of chemically induced tumours. The characteristic signs of chronic selenium exposure are abnormal hooves, horns and hair.

Alkali disease is the most characteristic manifestation from chronic exposure to selenium (via feed or selenium-accumulating plants) in large animals, such as cattle, steer and pigs (Zhang and Spallholz, 2011). It is characterized by emaciation, stiffness, lameness, loss of hair and cracking of hooves (O'Toole and Raisbeck, 1995). Heart and liver atrophy, anaemia and erosion of bones were also identified as symptoms of alkali disease (Moxon, 1937). Laboratory animals exposed chronically to doses of 0.1–0.57 mg/kg bw exhibited toxic effects characterized by weight loss, renal toxicity and liver toxicity (organ congestion, fatty degeneration of parenchymal cells, hyperplastic lesions, amyloidosis, nephritis, necrosis) (Nelson et al., 1943; O'Toole and Raisbeck, 1995; O'Toole et al., 1996; OEHHA, 2010).

Several chronic studies were undertaken to determine whether selenate or selenite induced tumours in laboratory animals. Schroeder and Mitchener (1971a) administered selenite or selenate in the drinking water at a concentration of 2 mg/L (0.14 mg/kg bw per day)[1] to Long-Evans rats at weaning. The dose was increased to 3 mg/L (0.21 mg/kg bw per day) at 1 year of age, and dosing continued until natural death occurred. Selenite's innate toxicity generated a high mortality rate among male rats, but a lower rate in females. Selenate did not induce any particular signs of toxicity during the first year. Toxic effects found at autopsy were increases in aortic plaques and serum cholesterol levels in both males and females. Rats fed selenate

[1] Assuming an intake of 7 mL water per 100 g bw.

developed more tumours than control rats (30 versus 20, $P \sim 0.001$) and more malignant tumours (20 versus 11, $P < 0.01$) than the controls, and at a younger age.

In contrast, there was no significant difference in tumour incidence when selenite or selenate was administered at 3 mg/L in drinking water to CD Swiss mice for life. However, reduced body weights in females, increased body weights in males and an obvious decline in general health were observed in the mice (Schroeder and Mitchener, 1972).

In a U.S. National Cancer Institute study conducted by Tinsley et al. (1967), 1437 rats of both sexes were divided among 34 different diet groups (food given *ad libitum*) supplemented with selenite or selenate at concentrations ranging between 0.5 and 16 mg/kg diet with varying protein concentrations for eight durations between 28 and 1150 days. Decreased feed consumption was seen at 4 mg/kg diet and above in males. Decreased growth rate was observed with increasing selenium dose. Selenate decreased body weight in a more pronounced way than did selenite in female rats. Toxic effects of selenium on almost all tissues autopsied, but mainly on the liver (focal lesions, abnormal cells), were observed from 0.5 to 16 mg/kg diet. Other affected organs included the adrenals (vesiculation of the cortex), pancreas (interstitial oedema, hyperplasia and congestion), myocardium (macrophage and lymphocyte infiltration and adventitial tissue proliferation), spleen (congestion, hyperplasia and depletion, reticulosis, sclerosis) and kidney (interstitial nephritis, presence of cysts). The only non-affected parameters were erythrocyte concentration and spleen weight. Higher protein content of the diet reduced the intensity of the lesions. Hyperplasic liver lesions did not disappear after selenium supplementation stopped. Tolerance to selenium (based on life length) was not induced by gradually increasing the selenite or selenate dose to 4 mg/kg diet in comparison with a direct administration of 4 mg/kg diet. A follow-up study analysing the tissues of these rats indicated no induction of neoplasms (Harr et al., 1967).

Another chronic study evaluated the effect of administering selenite in drinking water at a concentration of 1, 4 or 8 mg/L (10.3, 32.3 and 49.8 µg/day) to Swiss mice of both sexes for 47 weeks (Jacobs and Forst, 1981b). No significant effect was seen on survival at any dose. All animals gained weight; however, the 8 mg/L group gained only half of the weight gained by controls. No significant changes in serum chemistry (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase) were observed. No sign of neoplasia was observed in the groups.

9.2.4 Genotoxicity

The genotoxicity of selenium has been evaluated in a large variety of systems, and positive and negative results as well as protective effects have been noted (Ferguson et al., 2012). There is a large body of evidence suggesting that selenium prevents DNA damage *in vitro* and *in vivo* (Davis et al., 1999; Letavayová et al., 2006). Moreover, the element was shown to reduce the toxic effects of several carcinogens, including cadmium and arsenic, *in vitro* in animal and human cells (Davis et al., 1999; Zhou et al., 2009; Zwolak and Zaporowska, 2012).

Nevertheless, there is evidence that high doses of selenite and selenate can cause genotoxicity *in vitro* and *in vivo* based on various tests, such as the *Bacillus subtilis* rec-assay measuring DNA damage, the Ames *Salmonella* assay, chromosomal aberration measurements, the comet assay, the terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick end labelling (TUNEL) assay and recombination at meiosis based on crossover frequency in *Drosophila melanogaster* (Noda et al., 1979; Norppa et al., 1980a,b,c; Whiting et al., 1980; Ray, 1984; Khalil, 1989; WHO and FAO, 2004; Valdiglesias et al., 2009).

9.2.4.1 In vitro *findings*

The *in vitro* genotoxicity results are inconclusive and vary as a function of the concentration and form of selenium. Generally, higher concentrations and the species selenite generate positive results (Letavayová et al., 2006).

Different assays demonstrated the genotoxic potential of selenium. For example, selenate and, to a greater extent, selenite induced DNA damage in the *Bacillus subtilis* rec-assay (Nakamuro et al., 1976) and base-pair substitution in *Salmonella typhimurium* strains TA100 and TA104 (Noda et al., 1979; Kramer and Ames, 1988). Selenite and selenate have also shown DNA damage with Kada's rec-assay on *Bacillus subtilis* (Noda et al., 1979). In contrast, an absence of genotoxicity has been reported with the *Bacillus* and Ames *Salmonella*/microsome assays for selenite (Lofroth and Ames, 1978; U.S. EPA, 1991a; Valdiglesias et al., 2009).

Selenite was genotoxic and mutagenic by inducing gene conversion, back mutation, mitotic crossing-over, DNA double-strand breakage, frame-shift mutations and aberrant colony formation in the yeast *Saccharomyces cerevisiae* (Anjaria and Madhvanath, 1988; Letavayová et al., 2006). The genotoxic effects of selenite are hypothesized to be caused by the generation of reactive oxygen species (Letavayová et al., 2008). Also, the genotoxicity of selenite in yeast was enhanced by the addition of glutathione (Anjaria and Madhvanath, 1988). The reaction of selenite with glutathione generates reactive oxygen species, as detailed in Section 9.3 below (Mézes and Balogh, 2009).

Selenite, selenate and selenomethionine were genotoxic to primary human fibroblasts and purified peripheral blood lymphocytes, as measured by DNA fragmentation, chromosomal aberrations, DNA strand breaks, sister chromatid exchange and micronucleus induction (Lo et al., 1978; Ray and Altenburg, 1982; Khalil and Maslat, 1990). Selenite induced DNA damage and chromosomal aberrations (breaks and fragments) in cultured human fibroblasts, whereas selenate induced a weak increase in DNA repair (Lo et al., 1978). Also, selenite and selenomethionine induced chromosomal aberrations (fragments and breaks) and reduction of cell division in primary human lymphocytes (Khalil, 1989; Biswas et al., 2000). Selenite was more clastogenic than selenate. Selenite, selenate and selenide induced chromosomal aberrations and unscheduled DNA synthesis, as a measure of active DNA repair, in Chinese hamster ovary cells (Whiting et al., 1980). The effects were increased by the presence of S9 fractions and the addition of glutathione. The effects were attenuated by antioxidants such as superoxide dismutase, supporting the pro-oxidative effect of selenium, as explained in Drake (2006). The genotoxic effects in Chinese hamster ovary cells were not observed with organic selenium (selenocysteine, selenocystamine and selenomethionine).

In conclusion, the inorganic and selenomethionine forms of selenium have been demonstrated to be genotoxic *in vitro*, which is hypotesized to result from the increase in reactive oxygen species.

9.2.4.2 In vivo *findings*

The results from *in vivo* studies vary and do not demonstrate a clear genotoxicity pattern, although positive results have been observed at high concentrations (in the range of 0.15 mg/kg of food to near the LD_{50} of laboratory animals).

High selenite doses (5, 10 and 20 µmol/kg bw) injected intraperitoneally induced dose-dependent DNA strand breaks (comet assay) in hepatocytes of Sprague-Dawley rats (n = 5 male rats per dose) (Yu et al., 2006) and sister chromatid exchange and chromosomal aberrations in Chinese hamster (n = 20 of each sex) bone marrow (Norppa et al., 1980c). Norppa et al. (1980c) stated that at these high doses, three hamsters died a few hours after they had been injected with

selenium. Another study in male NMRI mice using the same protocol also found chromosomal aberrations in bone marrow cells, but not in primary spermatocytes (Norppa et al., 1980a).

Administration of selenite (0, 0.15 or 2.0 mg/kg of food) for 10 weeks in the diet of Sprague-Dawley rats induced a dose-dependent increase in 8-hydroxy-2′-deoxyguanosine (8-OHdG), an indicator of oxidative DNA damage (Wycherly et al., 2004). This supports the *in vitro* studies showing the involvement of reactive oxygen species in the induction of DNA damage.

Also, 49 elderly (corresponding to 62- to 69-year-old men) male beagle dogs were fed for 7 months with a normal diet or diet supplemented with selenomethionine or selenium-enriched yeast at an adequate (3 µg/kg bw) or supranutritional (6 µg/kg bw) level (Waters et al., 2003, 2005). DNA strand breaks in cells from the brain and the prostate (> 90% epithelial cells), evaluated by the comet assay, revealed a non-linear DNA damage response—i.e., a U-shape in relation to the dose (Waters et al., 2005). In an earlier publication by the same group using the same protocol, a decrease in DNA damage (comet assay) and an increase in apoptosis (TUNEL assay) were measured (Waters et al., 2003).

In humans, selenite injected or given in oral tablets (0.004–0.050 mg/kg bw per day for 1–13.5 months) did not induce chromosomal aberrations in lymphocytes (Norppa et al., 1980c).

In conclusion, genotoxicity and oxidative effects, or protection against them *in vitro* and in animals, caused by organic and inorganic selenium vary depending on the dose, the test system and the test method used. Although genotoxicity is observed *in vitro* and *in vivo*, the evidence does not suggest that selenium is directly genotoxic. The positive results observed at high doses are hypothesized to be caused by the generation of reactive oxygen species, and not by the direct action of selenium on the DNA, as demonstrated by the increase in 8-OHdG (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2000; Drake, 2006; Letavayová et al., 2006, 2008).

9.2.5 Reproductive and developmental toxicity

Limited studies on the reproductive and developmental toxicity of selenium were found in the literature. The few cases of reproductive and developmental toxicity observed in laboratory animals are associated with maternal toxicity.

9.2.5.1 Reproductive effects

Rosenfeld and Beath (1954) exposed rats for two generations to inorganic selenium as selenate in their drinking water at a concentration of 1.5, 2.5 or 7.5 mg/L (dose not specified by the authors). No adverse effects on reproduction were observed in rats exposed to 1.5 mg/L in drinking water. In the 2.5 mg/L group, however, maternal toxicity (loss of weight, increased mortality) was observed as well as a 50% reduction in the fecundity and fertility of the females. At the high dose (7.5 mg/L), growth and survival of pups were adversely affected. No histological examination of the reproductive organs was done.

Sprague-Dawley rats were exposed to selenate in drinking water at 0, 7.5, 15 and 30 mg/L (estimated to be equivalent to doses of 0, 0.5, 0.8 and 1.1 mg/kg bw per day) for 30 days (n = 10–13 rats of each sex per dose group) (NTP, 1996). Female rats were divided among three groups: peri-conception, gestational and vaginal cytology. Maternal and male body weights were reduced in all selenate dose groups. Reproductive functions (decreases in number and weight of live pups, number of implants and pup survival) were altered only at 1.1 mg/kg bw per day. Only minor effects on male reproductive functions were noted (changes in testicular and epididymis weights at 0.8 and 1.1 mg/kg bw per day). Selenate was not considered a reproductive or

developmental toxicant, as it decreased body weight at doses below that at which it affected reproduction.

Water containing selenate at a concentration of 3 mg/L was administered *ad libitum* to three generations of CD mice. Selenium increased the number of runts and failures to breed in the three generations (Schroeder and Mitchener, 1971b).

Male BALB/c mice were subjected to a Baker's yeast diet supplemented with varying concentrations of selenite (0–1.02 mg/kg) for 4 or 8 weeks (Shalini and Bansal, 2008). Number of spermatozoa and sperm motility were decreased, whereas lipid peroxidation in testis, DNA strand breaks, flagellar defects and fusion of the mid-piece of the sperm were increased at selenite levels considered by the authors to be deficient (0.02 mg/kg) or in excess/supranutritional (1.02 mg/kg), compared with the level considered to be adequate (0.22 mg/kg). Degenerating mitochondria, improper chromatin condensation and DNA strand breaks of the sperm (at 4 weeks) were significantly increased at 0.02 mg/kg (deficient level) compared with excess and adequate levels. The effects were generally more pronounced after 8 weeks. No other health effects were reported by the authors.

A study was conducted on the reproductive ability of male BALB/c mice subjected to a Baker's yeast diet supplemented with varying concentrations of selenite (0–1.02 mg/kg) for 8 weeks (Kaur and Bansal, 2005). Only the mice fed a selenium-deficient diet (0.02 mg/kg) showed a significant decrease in the number of pachytene spermatocytes and young and mature spermatids, in sperm number and in fertility status in comparison with the control mice fed a diet with selenium levels considered adequate (0.2 mg/kg). The mice fed a diet with excess/supranutritional selenium (1.02 mg/kg) had no significant differences in these parameters compared with the control mice.

The increase in lipid peroxidation was observed in another study by the same author using the same protocol of mice exposure (Shalini and Bansal, 2007). Decreases in fertility ($P < 0.001$) and litter size ($P < 0.05$) were observed in mice fed a diet with excess/supranutritional selenium (1.02 mg/kg). Increases in NF-κB and nitric oxide (inflammatory indicator) were observed in the selenium-deficient mice only.

High levels of selenite ingested in the diet (2 or 4 mg/kg) by rats for 5 weeks reduced body weight, testicular and caudal epididymis weights and spermatozoid viability, whereas exposure to 4 mg/kg caused a decrease in sperm motility and an increase in abnormalities of the mid-piece region of spermatozoids (Kaur and Parshad, 1994). High variability in sperm abnormality was observed between individual rats.

Selenate in drinking water is not considered to be a reproductive/developmental toxicant, as it decreased rat body weight at doses below that at which it affected reproduction in the NTP study.

9.2.5.2 Developmental effects

Maternal exposure to selenium in drinking water at a concentration of 3 or 6 mg/L did not produce teratogenicity. Retardation of fetal growth was reported when female IVCS mice were given high doses of selenite (6 mg/L) in drinking water 30 days before and 15 days during pregnancy. The study also showed no difference in litter size between the selenium groups. No maternal effects were reported by the authors (Nobunaga et al., 1979).

One study found malformations of offspring after oral selenite (4–19 mg/kg bw) or selenate (17–21 mg/kg bw) administration to pregnant hamsters (Ferm et al., 1990). However, this was associated with severe maternal toxicity (weight loss and exhaustion), leading to a 50% mortality of the animals at the oral selenite dose of 19 mg/kg bw. The increase in encephaloceles (common in this strain) of the fetus and decreased fetal crown–rump length are associated with a

decrease in the mother's body weight and/or feed consumption at either single or repeated treatment. As maternal general malnutrition and weight loss are risk factors for developing fetal abnormalities, no conclusion on selenium teratogenicity can be drawn from this study.

Four monkeys were fed a basal semipurified diet supplemented with selenite (200 µg/kg) in their last 2–4 months of pregnancy. The juveniles showed no sign of abnormalities. The female monkeys were rebred and gave birth to another set of four healthy infants (Butler et al., 1988).

Female rats fed supranutritional selenium levels in the diet (selenite at 3 or 4.5 mg/kg) for 8 weeks prior to mating had normal fetal development (Bergman et al., 1990).

In summary, selenium has been shown to cause some reproductive and developmental toxicity in laboratory animals (rats and mice); however, the results are inconsistent across studies, and no conclusions can be drawn.

9.3 Mode of action

The research on the mode of action of selenium is focused mainly on the beneficial and anticarcinogenicity potentials of the element. Its toxicity mechanisms remain unclear and probably result from multiple metabolic pathways. The perturbation of the cell oxido-reduction equilibrium by the decrease in the glutathione/glutathione disulphide ratio, a rise in oxidative events and the replacement of sulphur atoms in proteins lead to toxic effects such as nail and hair abnormalities (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2000; Zhong and Oberley, 2001; Nogueira and Rocha, 2011; Zhang and Spallholz, 2011).

9.3.1 Toxic effects

The molecular mechanisms of the toxicity of selenium remain unclear, and it is suggested that multiple events operate (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2006). Selenium toxicity is largely mediated by its pro-oxidant effect, leading to the production of hydrogen peroxide and reactive oxygen species involved in tissue damage (Spallholz, 1997; Letavayová et al., 2008; Brozmanová et al., 2010). This would result from a depletion in glutathione, *S*-adenosylmethionine (a precursor of aminopropyl groups and glutathione; it also regulates the activities of multiple enzymes) and levels of vitamin E in the liver (Anundi et al., 1984; Scarlato and Higa, 1990; Expert Group on Vitamins and Minerals, 2003; EFSA Panel on Dietetic Products, Nutrition and Allergies, 2006; Tiwary et al., 2006). In fact, incubation of yeast with 0.25 mmol/L selenomethionine decreased thiol compounds and cell growth. The adverse effects were reversed by the addition of cysteine (Kitajima et al., 2012). Moreover, incubation of hepatocytes with low levels of selenite (30–100 µmol/L) induced an increase in oxygen consumption and oxidized glutathione and a depletion of the electron donor nicotinamide adenine dinucleotide phosphate (NADPH) (Anundi et al., 1984; Kim et al., 2004). In another study, mice were injected with selenite at a dose of 5 nmol/g bw. A marked decrease in adenosylmethionine in the liver was measured, and the inhibition of the methionine adenosyltransferase was suggested as the mechanism of action (Hoffman, 1977). This also leads to a depletion of the sulphydryl group in the liver. The duality of selenium potentially acting as an antioxidative and an oxidative agent was demonstrated in a human hepatoma cell line exposed to selenite in the presence or absence of glutathione inducing/inhibiting compounds (Shen et al., 2000).

Also, both organic and inorganic selenium can interact with sulphur in critical sulphydryl groups within proteins and other molecules, such as glutathione (Spallholz, 1997). This can also lead to the formation of reactive intermediary compounds, such as selenotrisulphides and methylselenide, which react with other thiols, leading to a decrease in glutathione both *in vitro*

and in animals, followed by the generation of the superoxide anion and hydrogen peroxide (Spallholz, 1997; Nogueira and Rocha, 2011; Zhang and Spallholz, 2011). Accordingly, selenium inhibits thiol-containing enzymes, such as methionine adenosyltransferase, succinate dehydrogenase, lactate dehydrogenase and NADP+-isocitrate dehydrogenase (Mézes and Balogh, 2009). The decrease in thiol-containing antioxidant proteins can also result in an indirect generation of reactive oxygen species (Mézes and Balogh, 2009). The increase in reactive oxygen species can lead to a cascade of events, including lipid peroxidation, DNA damage and loss of membrane integrity and permeability (e.g. organelle membrane), leading to lysosomal enzyme release and tissue necrosis (Mézes and Balogh, 2009).

Another theory on the mechanism of toxicity suggests that high levels of selenium result in the replacement of sulphur by selenium (Letavayová et al., 2006). For example, selenium can cause inadequate incorporation of sulphur into amino acids, such as in critical sulphydryl groups of glutathione involved in antioxidant defences (Pickrell and Oehme, 2002). This can inhibit protein synthesis and the function of DNA repair proteins.

Tests done *in vitro* on tumour cells support the involvement of oxidative events, which may not be specific to cancer cells, in selenium-induced toxicity. The increased production of reactive oxygen species and induction of apoptosis have been observed *in vitro* in different cancer cell lines (Yoon et al., 2001; Drake, 2006; Guan et al., 2009; Kandas et al., 2009).

The potentially increased risk of diabetes in response to high intakes of selenium is thought to be caused by an excessively high level of antioxidative activity (Steinbrenner, 2011). This would remove hydrogen peroxide, normally acting as an intermediate (second messenger) in the mechanism of pancreatic insulin secretion and in the signal transduction in response to insulin binding to its receptor. Hence, high levels of antioxidant induced by selenium could potentially impair insulin sensitivity.

9.3.2 Beneficial effects

Paradoxically, the beneficial effects of selenium are due, on one hand, to its involvement in antioxidant defences through its incorporation into selenium-dependent enzymes, such as glutathione peroxidase, and, on the other hand, to its pro-oxidant effects, leading to the apoptosis of cancer cells (Valdiglesias et al., 2009). The chemical form of selenium influences its biological activity; organic forms are generally less toxic, being incorporated more easily into selenoproteins (Chen et al., 2000; Spallholz, 2001; Yan and DeMars, 2012). However, both organic and inorganic selenium compounds increase the activity of glutathione peroxidase and the cellular antioxidative potential *in vitro* and *in vivo* (Dalla Puppa et al., 2007; Erkekoğlu et al., 2011; de Rosa et al., 2012; Moon et al., 2012).

There is consensus that selenium is an essential element (Foster and Sumar, 1997; Expert Group on Vitamins and Minerals, 2002; CCME, 2009; EFSA Panel on Dietetic Products, Nutrition and Allergies, 2010; WHO, 2011). It is involved in antioxidant defences, the regulation of immune and endothelial cell functions and the regulation of thyroid hormones by being an integral part of various selenoproteins (Zeng et al., 2009). These directly participate in DNA transcription, protein synthesis and maturation, calcium flux and oxidant scavenging (Forceville, 2006). Selenium has also been shown to antagonize the oxidative effects of other metals, such as mercury. Selenomethionine counteracted the decrease in superoxide dismutase and glutathione and the increase in malondialdehyde observed in rats exposed to mercury (Su et al., 2008). Preincubation of C6 glioma cells with 50 µmol/L selenomethionine reduced the levels of reactive oxygen species caused by mercury (Kaur et al., 2009). Likewise, selenite (10 µg/L) protected against the decrease of activity of the thioredoxin reductase in the liver of zebra seabream fish (n = 78) (Branco et al., 2012). Selenoprotein activity is dependent on the presence of the amino

acid selenocysteine at the catalytic site. Plasma selenium concentrations of 70–90 µg/L are considered adequate for enzyme function (Institute of Medicine, 2000). Selenium deficiency leads to malfunctioning of many systems, resulting in inflammation, atherosclerotic diseases and perhaps an increased prevalence of chronic diseases (Turner and Finch, 1991; Kohrle and Gartner, 2009).

Preincubation of human endothelial cells for 24 hours with sodium selenite at 5–40 nmol/L provided significant protection against the oxidative effects of *tert*-butylhydroperoxide (Miller et al., 2001). The activities of cytoplasmic glutathione peroxidase (GPX-1), phospholipid hydroperoxide glutathione peroxidase (GPX-4) and thioredoxin reductase were also each induced by selenite (Miller et al., 2001). Preincubation with low concentrations of selenite (30 nmol/L) or selenomethionine (10 nmol/L) protected LNCaP prostate cancer cells from oxidative DNA damage (comet assay) induced by ultraviolet-A or hydrogen peroxide (de Rosa et al., 2012).

Prevention mechanisms of cancer are incompletely understood. Selenium's anticarcinogenic effects are hypothesized to be mediated through multiple mechanisms (Stewart et al., 1997; Redman et al., 1998; Drake, 2006; Jackson and Combs, 2008; Valdiglesias et al., 2009). For example, selenium can alter the expression of phase I and II detoxifying enzymes, inhibit adduct formation, induce apoptosis of cancer cell lines and act as an antiproliferative and antioxidant agent (Lawson and Birt, 1983; McCarty, 1998; Davis et al., 1999; Keck and Finley, 2004; Letavayová et al., 2006; Guan et al., 2009; Jariwalla et al., 2009; Wang et al., 2009). Selenoproteins are thought to be an important element in cancer protection (Diwadkar-Navsariwala et al., 2006; Zeng et al., 2009).

Various tests were done on tumour cells demonstrating that oxidative stress is involved in apoptosis induction. For example, selenite induced a dose-dependent depletion of glutathione and an increase in apoptosis (cell detachment and DNA fragmentation, measured based on the TUNEL assay) at concentrations from 1 to 100 µmol/L (Stewart et al., 1997). Oxidative stress–induced apoptosis was also observed in human hormone-dependent prostate adenocarcinoma cells (LNCaP) and in the Cheng liver cell line exposed to high doses of selenite (Zhong and Oberley, 2001; Kim et al., 2004; Kandas et al., 2009). Also, apoptosis, through an increased production of reactive oxygen species and phosphorylation of p53 (induction of apoptosis in response to DNA damage), mitochondrial depolarization and caspase cleavage were observed in human leukaemia NB4 cells exposed to selenite (Guan et al., 2009). In fact, selenite and methylselenol are pro-oxidants involved either directly or indirectly in the oxidation of enzyme cysteine clusters, such as protein kinase C and glutathione. The direct oxidation of the catalytic centre of protein kinase C by selenite has been shown to induce apoptosis (Drake, 2006). Moreover, the reaction of selenite with glutathione produces the selenide anion (CH_3Se^-), which may react with oxygen to produce the free radical $O_2\cdot^-$. The increase in production of reactive oxygen species causes a diminution of the glutathione pool, an increase in DNA damage and apoptosis (Drake, 2006; Letavayová et al., 2006).

Adding antioxidants to the cell media *in vitro* has been shown to inhibit cell mammary tumour cell death induced by selenite (Zhong and Oberley, 2001). Although these are thought to be beneficial effects, in that they inhibit cancer cell growth, they are supportive of the toxic oxidative potential of selenium compounds in normal cells (Zhang and Spallholz, 2011).

Randomized trials across a wider range of selenium status would help determine the optimal levels of selenium intake in the general population to maximize health benefits while avoiding potential chronic toxic effects. Also, optimal intake for any individual is likely to depend on polymorphisms in selenoprotein genes, which may also affect the risk of disease, including coronary heart disease and ischaemic stroke (Alanne et al., 2007; Rayman, 2012).

Future work in the field examining the effect of selenium supplements on chronic disease should give attention to the potential interaction between genetic make-up and selenium intake or status.

9.3.2.1 Selenium protection against tumour formation in animals

In several species, selenium has been shown to inhibit the number and size of tumours induced chemically and to delay their age of onset (Jacobs, 1980; Jacobs and Forst, 1981a; Ankerst and Sjogren, 1982; Lane and Medina, 1985; Ip et al., 1991, 2000; U.S. EPA, 1991a; Woutersen et al., 1999; ATSDR, 2003; WHO, 2011).

In order to demonstrate that selenium protects against cancer, inbred female C3H/St mice, a strain that develops mammary adenocarcinomas at high frequency, were dosed with various concentrations of selenite in water over a lifetime, accompanied by selenium-rich or selenium-poor diets. Groups of mice that received selenite at 0.0, 0.1, 0.5 or 1.0 mg/L in water, with a protein-enriched Wayne diet (selenium concentration of 0.45 mg/kg), had a reduced tumour incidence and an increase in the age of the mice at tumour appearance (i.e., delayed tumour onset) in a dose-dependent fashion (Schrauzer et al., 1978). In another study, a group of mice receiving a low-protein Concord diet (selenium concentration of 0.15 mg/kg) had a reduction in tumour size, growth rate and malignancy when selenium was added to drinking water at 0.1, 0.5 or 2.0 mg/L compared with controls (Schrauzer et al., 1978).

Regarding chemically induced tumours, 55-day-old Sprague-Dawley rats were injected intraperitoneally with the mammary carcinogen methylnitrosourea at 50 mg/kg bw (Ip et al., 2000). A diet with either a basal level of selenium in the form of selenite (0.1 mg/kg) or a supplemented diet including methylselenocysteine (3 mg/kg) or the synthetic water-soluble triphenylselenonium chloride (30 mg/kg) was then administered for 6 weeks. Compared with the controls receiving the basal diet (0.1 mg/kg as selenite), methylselenocysteine reduced the total number of mammary premalignant intraductal lesions by 60% (23 lesions versus 57 in the controls). However, methylselenocysteine had no effect on the proliferation potential of those premalignant cells, revealed by cell cycle biomarkers (proliferating nuclear antigen, cyclin D1, replication of DNA). In the methylselenocysteine group, an increase in p27/Kip 1 protein was observed, which may play a role in tumour prevention, considering the protein's inhibitory action on cell cycle transition and its promotion of differentiation. Conversely, triphenylselenonium chloride (30 mg/kg) reduced the number of larger size lesions and cell proliferation.

An increase in activity of the antioxidant enzyme glutathione peroxidase can be involved in preventing cancer and other chronic diseases (Nogueira and Rocha, 2011). Both organic and inorganic selenium (selenite) have increased glutathione peroxidase activities and blood selenium concentrations in six female rhesus monkeys exposed to 0.25–0.5 µg/mL for 11 months (Butler et al., 1990).

In conclusion, selenium has not been shown to be carcinogenic in animal studies. Alkali disease is the most common manifestation from chronic exposure to selenium in large animals, such as cattle, steer and pigs (Zhang and Spallholz, 2011).

9.3.3 Comparison between the effects of organic and inorganic selenium species

Most of the available epidemiological literature is on exposure to organic species of selenium naturally present in food, rather than to the inorganic species. Detailed studies on the mechanistic differences between inorganic and organic selenium species are scarce. Although detailed studies in which animals are exposed to inorganic species exist, more confidence is placed in the human data on exposure to organic selenium, as explained below.

The current body of evidence suggests that organic and inorganic selenium species generally have similar health effects and share some metabolic pathways in humans. As such, both organic and inorganic selenium compounds are metabolized to selenide and incorporated into selenoproteins (Gromadzińska et al., 2008; Rayman, 2012). Preincubation with low concentrations of selenite (30–500 nmol/L) or selenomethionine (10 nmol/L) protected microglial or LNCaP prostate cancer cells from oxidative DNA damage (comet assay) induced by ultraviolet-A, phthalates or hydrogen peroxide (Dalla Puppa et al., 2007; Erkekoğlu et al., 2011; de Rosa et al., 2012). Selenite and selenomethionine did not have a significant effect in terms of change in body weight, tumour weight, apoptosis induction or tumour angiogenesis when administered orally at 3 mg/kg bw in athymic mice that had been injected with a xenograft of epithelial cancer cells, whereas methylseleninic acid decreased cancer growth (Li et al., 2008).

The speciation and metabolism differences between inorganic and organic forms of selenium have recently been highlighted in a review (Weekley and Harris, 2013). Although both forms can be metabolized to a common metabolite (selenide), they differ in their reduction pathways. Studies on cancer cell apoptosis have shown that selenite reduction is associated with an increase in reactive oxygen species (ROS) production at high level of exposure, while organic selenium follows more complex schemes of trans-sulfuration and methylation involving many lyases. All dietary forms of selenium have been shown to generate a variety of ROS and to increase radical scavenging activity (antioxidant selenoproteins). The authors suggest that more information is needed to understand the biological relevance of the differences in metabolism pathways, although their focus is on disease prevention and/or treatment.

Organic and inorganic species increase glutathione peroxidase activity and reduce levels of reactive oxygen species *in vitro* and *in vivo* when administered orally to experimental animals or humans (Thomson et al., 1982; Pehrson et al., 1999; Dorea, 2002; Kaur et al., 2005; Xia et al., 2005; Gromadzińska et al., 2008; Abedelahi et al., 2010). Moreover, Keshan disease was prevented in Chinese individuals supplemented with selenite (Yang, 1984; Cheng and Qian, 1990).

In addition, both organic and inorganic selenium species deplete thiol compounds such as glutathione and induce oxidative stress and selenosis symptoms *in vitro* and *in vivo* in humans and experimental animals at high doses (O'Toole and Raisbeck, 1995; Reid et al., 2004; Griffiths et al., 2006; Forceville, 2007; MacFarquhar et al., 2010; Kitajima et al., 2012; Misra et al., 2012). Both selenite and selenomethionine at 1 µmol/L interfered with the reactive oxygen species–induced cascade of phosphorylation in muscle cells in response to insulin (Pinto et al., 2011). However, as described in Section 9.2, some differences in effects have also been observed between inorganic and organic selenium species. These could differently affect genetic expression, as demonstrated by the variations in gene expression levels (measured in the gastrocnemius muscle, cerebral cortex and liver with the microarray assay) induced in mice by adding 1 µg/kg bw of selenite, selenomethionine or selenium-enriched yeast to food for 100 days (Barger et al., 2012). However, mechanistic studies documenting the differences between the effects of selenium species are lacking, and no definitive conclusions can be drawn at the present time.

10.0 Classification and assessment

Selenium has been classified by the International Agency for Research on Cancer in Group 3: not classifiable as to its carcinogenicity to humans (IARC, 1975). The vast majority of epidemiological and animal studies do not demonstrate an increase in cancer incidence following a wide range of chronic exposures to selenium via food or supplements; a protective effect has

even been suggested (Harr et al., 1967; Klein et al., 2003; Longtin, 2003; WHO, 2011; Ferguson et al., 2012).

Selenium is an essential nutrient and a component of several proteins and enzymes in the body that are known to play important roles, including regulation of thyroid hormones and antioxidant defences (Institute of Medicine, 2000; Otten et al., 2006). A deficiency in selenium may lead to chronic diseases such as Keshan disease (characterized by cardiomyopathy) and Kashin-Beck disease (characterized by rheumatism) (Yang, 1984) and may also be associated with a form of cretinism related to hypothyroidism (Spallholz, 2001; WHO and FAO, 2004; Xia et al., 2005). In order to protect the Canadian population from the aforementioned diseases, Health Canada adopted the RDA for selenium established by the Institute of Medicine (2000). These recommended daily intakes vary between 15 and 55 µg of selenium per day, depending on the age group. Selenium deficiency is not likely to be a concern in Canada, as the estimates from the Canadian TDS (2005–2011) show that the Canadian population meets the Institute of Medicine's recommended daily intake from food, which represents the main source of selenium.

Selenium toxicity generally occurs when exposure levels are much higher than the recommended daily intakes. Selenosis symptoms resulting from chronic exposure to high levels of selenium are characterized by hair loss, nail anomalies or loss, skin anomalies, garlic odour of the breath, tooth decay and, more severely, disturbances of the nervous system.

The studies of Yang and colleagues focus on the symptoms of selenosis in a Chinese population (Enshi County) exposed to high levels of selenium (Yang et al., 1989a,b) and the follow-up of five recovered sensitive individuals from the same population (Yang and Zhou, 1994). The source of selenium was mainly food (plant based) (Yang et al., 1983). The level of intake was classified as low, medium or high and estimated through questionnaire distribution and measurements of selenium in food items. Selenosis symptoms were classified according to their severity (Yang et al., 1989b). Symptoms were not present in individuals with a blood selenium concentration of 1000 µg/L or below. Blood selenium levels in the range of 1000–2000 µg/L induced symptoms in up to 35% of individuals, whereas blood selenium concentrations in the range of 2000–3300 µg/L or higher induced symptoms in 45% of individuals. Symptoms were mainly (97% of the time) present in adults. Persistent selenosis symptoms were observed in five Chinese individuals with blood selenium concentrations ranging between 1054 and 1854 µg/L. The authors calculated that a blood selenium concentration of 1054 µg/L corresponded to an intake of 910 µg/day and identified these as the minimum blood selenium concentration and selenium intake causing toxicity, respectively. The authors also indicated that the maximum daily safe intake of selenium was 750–850 µg/day.

After their diet was improved, those same five patients participated in a follow-up study (Yang and Zhou, 1994). By 1992, their symptoms had disappeared, and their blood selenium concentrations had dropped from an average of 1346 µg/L to 968 µg/L, the latter representing a mean intake of 819 µg/day, which was identified as the NOAEL by the authors. After taking into account interindividual variations, the authors identified a safe maximum daily intake of 400 µg/day (corresponding to a blood selenium concentration of 0.559 mg/L).

Although the key studies of Yang and colleagues (Yang et al., 1989a,b; Yang and Zhou, 1994) have some limitations, they provide qualitative and quantitative information useful for the dose–response assessment and risk characterization of selenium associated with high levels of intake. The absence of symptoms in other populations with high dietary levels of selenium exposure is supportive of the use of the NOAEL identified by Yang and colleagues and the Institute of Medicine (Otten et al., 2006) as a basis for the risk assessment. Findings from the studies by Longnecker et al. (1991) and Lemire et al. (2012), also performed in areas with high levels of selenium, confirm the findings from the studies by Yang and colleagues, as selenosis

symptoms were not observed at exposure levels up to 724 µg/day and blood selenium concentrations up to 1500 µg/L, respectively. The UL derived by the Institute of Medicine is based on the adult subpopulation, as selenosis is a chronic health effect and no selenosis symptoms were observed in children in the Chinese, Venezuelan or Amazonian studies (Institute of Medicine, 2000). The Institute of Medicine (2000) stated that there is no known seleniferous area in Canada or the United States with recognized cases of selenosis.

Some epidemiological studies and clinical trials have reported associations between high selenium exposure and potential adverse health effects. The results of the NPC trial (Stranges et al., 2007) and the SELECT trial (Klein, 2009; Lippman et al., 2009) suggest a potential association between selenium intake and diabetes risk in a selenium-replete population, such as the one in the United States. A few epidemiological studies have also found an association between selenium exposure and other diseases, such as ALS (Vinceti et al., 2010) and glaucoma (Bruhn et al., 2009). Although these endpoints are important and might be linked to selenium intake, the generalizability of their results to the Canadian population is questionable and limited. These studies would also need to control for many biases and confounding factors involved in the development of these diseases (Health Canada, 2012b; Thayer et al., 2012). Trials designed to measure the effects of selenium exposure on specific diseases have to be conducted before conclusions can be drawn.

The UL, which is the highest level of nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population, was calculated by the Institute of Medicine (IOM, 2000) as follows:

$$UL = \frac{NOAEL}{UF}$$

$$= \frac{800\ \mu g/day}{2}$$

$$= 400\ \mu g/day$$

where:

- 800 µg/day is the NOAEL (rounded by IOM, 2000) established by Yang and co-workers (Yang et al., 1989a,b; Yang and Zhou, 1994);
- 2 is the uncertainty factor chosen by IOM (2000) to protect sensitive individuals. IOM explains their selection of this non-conventional uncertainty factor based on the need for an uncertainty factor higher than 1 to account for the non-severe nature of the toxic effect and the fact that it may not be readily reversible.

Health Canada (2010b) has adopted IOM's UL of 400 µg of selenium per day. According to IOM (2000), there is no evidence indicating an increased sensitivity to selenium toxicity for any age group.

Using this UL, the health-based value (HBV) for selenium in drinking water is derived as follows:

$$HBV = \frac{0.4\ mg/day \times 0.20}{1.5\ L/day}$$

= 0.053 mg/L (~50 µg/L)

where:

- 0.4 mg/day is the UL, as derived by IOM (2000);
- 0.20 is the default allocation factor for drinking water; it is used as a "floor value," since drinking water is not a major source of exposure to selenium, and there is evidence of the widespread presence of selenium in one of the other media (i.e., food) (Krishnan and Carrier, 2013); and
- 1.5 L/day is the daily volume of water consumed by an adult.

10.1 International considerations

The U.S. EPA's Integrated Risk Information System has classified selenium as not classifiable as to its carcinogenicity in humans (class D) based on inadequate human data and inadequate evidence of carcinogenicity in animals (U.S. EPA, 1991a). As an exception for selenium compounds, selenium sulphide and selenium disulphide are classified by the U.S. EPA as class B2: probable human carcinogens based on sufficient animal data and inadequate human data, based on a comprehensive gavage study in mice and rats (NCI and NTP, 1980; U.S. EPA, 1991b). As these compounds are not soluble in water (ATSDR, 2003) and as the primary routes of exposure to these compounds are dermal and inhalation, they are not relevant to the risk assessment for selenium in drinking water.

Other organizations have set guidelines or regulations pertaining to the concentration of selenium in drinking water based on either the Chinese (Yang and Zhou, 1994) or the American (Longnecker et al., 1991) population studies or directly on the Institute of Medicine's UL of 0.4 mg/day (which is based on the Chinese population studies).

The current U.S. EPA maximum contaminant level (MCL) for selenium is 50 µg/L, which, for this particular compound, equals the maximum contaminant level goal (MCLG), "because analytical methods or treatment technology do not pose any limitation" (U.S. EPA, 2012). The MCLG (U.S. EPA, 1991a) was based on the Chinese data from Yang et al. (1989a,b). As part of its 6-year review, the U.S. EPA (2012) determined that the "MCL and MCLG for selenium are still protective of human health."

The California Office of Environmental Health Hazard Assessment (OEHHA, 2010) established a public health goal (PHG) of 30 µg/L for selenium in drinking water. The calculation of this PHG considered the NOAEL (0.015 mg/kg bw per day) for toxic non-cancer effects (hair loss and nail damage) observed in Chinese population studies. California's current standard (MCL) for selenium is 50 µg/L, which was adopted by the California Department of Health Services in 1994. It is based on the 1991 U.S. EPA rule.

The World Health Organization (WHO, 2011) established a provisional drinking water guideline value of 40 µg/L based on the Institute of Medicine's UL of 0.4 mg/day, an allocation factor of 20% and a consumption of 2 L of drinking water per day. The provisional designation was based on uncertainties inherent in the scientific database. It was noted that a drinking-water guideline for selenium would be unnecessary for most Member States and that achieving a proper balance between recommended intakes and undesirable intakes was essential to consider in establishing the guideline value.

The Australian drinking water guideline for selenium is 10 µg/L (NHMRC and NRMMC, 2011) based on the absence of effects associated with an average selenium intake of 0.24 mg/day by individuals living in a high-selenium region of South Dakota and eastern Wyoming over a 2-year period (Longnecker et al., 1991). The guideline value was based on a 10% allocation factor and assuming a 70 kg adult drinking 2 L of water per day.

11.0 Rationale

Selenium is an essential nutrient that is naturally occurring and found mostly in the Earth's crust. The main sources of selenium in the environment include coal-fired power plants and mining and refining of metals. Selenium is used in a wide range of industries to produce glass and electronic materials and to replace lead in plumbing. Canadians are mainly exposed to selenium through the consumption of food and nutritional supplements. Other organizations, such as the Institute of Medicine, have established daily recommended intakes for selenium, but selenium deficiency is not considered to be a concern in Canada. Exposure data do not indicate significant levels of selenium in Canadian drinking water supplies.

The International Agency for Research on Cancer has determined that selenium is not classifiable as to its carcinogenicity to humans. A protective effect against cancer has even been suggested. Selenium toxicity or selenosis can occur at exposure levels much higher than the recommended daily intake. The maximum acceptable concentration (MAC) for selenium in drinking water is based on chronic selenosis symptoms, such as hair loss, nail anomalies or loss, skin anomalies and garlic odour of the breath. These symptoms have been observed in adults, and there is no evidence of an increased sensitivity to selenium toxicity in any other subgroup of the population.

A MAC of 0.05 mg/L (50 µg/L) is established for total selenium in drinking water. This MAC is achievable by available treatment technology and measurable by available analytical methods. As part of its ongoing guideline review process, Health Canada will continue to monitor new research in this area and recommend any change to the guideline that it deems necessary.

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Appendix A: List of acronyms

8-OHdG	8-hydroxy-2′-deoxyguanosine
ALS	amyotrophic lateral sclerosis
ANSI	American National Standards Institute
BAT	best available technology
bw	body weight
CI	confidence interval
CSA	Canadian Standards Association
DNA	deoxyribonucleic acid
EBCT	empty bed contact time
EPA	Environmental Protection Agency (U.S.)
EPIC	European Prospective Investigation into Cancer and Nutrition
gpm	gallons per minute
HBV	health-based value
HR	hazard ratio
LD_{50}	median lethal dose
MAC	maximum acceptable concentration
MCL	maximum contaminant level (U.S.)
MCLG	maximum contaminant level goal (U.S.)
MDL	method detection limit
ND	not detected
NHANES	National Health and Nutrition Examination Survey (U.S.)
NOAEL	no-observed-adverse-effect level
NPC	Nutritional Prevention of Cancer
NSF	NSF International
NTP	National Toxicology Program (U.S.)
OR	odds ratio
PHG	public health goal (U.S.)
PQL	practical quantification limit
RDA	recommended dietary allowance
RO	reverse osmosis
RR	relative risk
SCC	Standards Council of Canada
SELECT	Selenium and Vitamin E Cancer Prevention Trial
SEM	standard error of the mean
SMR	standardized mortality ratio
TDI	tolerable daily intake
TDS	Total Diet Study
TUNEL	terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick end labelling
UF	uncertainty factor
UL	tolerable upper intake level