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Health and Ecological Effects of Selenium

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Health and Ecological Effects of Selenium

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ABSTRACT

Selenium is a naturally occurring element that can be found at background levels in food, soil, and water. It is also present in coal combustion products (CCPs) and CCP leachate. While selenium is essential to human and animal life, it has the potential to cause toxicity to humans and other organisms above a certain threshold level. This report summarizes the adverse human and ecological effects that can potentially occur from overexposure to selenium and the levels at which the effects can occur, with particular emphasis on ecological effects that may be associated with selenium in CCPs.

The primary route of exposure to selenium in the United States is through food consumption. The average intake of selenium per person in the United States ranges from 0.071 to 0.152 mg/day. Selenium is an essential nutrient required for normal function, growth, and reproduction. The recommended daily allowance of selenium is 0.055 mg/day for male and female adults (approximately 0.8 µg/kg-day). There is a wealth of literature describing the beneficial effects of selenium on human health, including an association with reduced cancer incidence at recommended dietary intake levels. Selenium is also known to counteract the toxic effects of some other metals (for example, arsenic, mercury, lead, cadmium, and silver). There is no evidence to suggest that selenium is a human carcinogen. Acute oral exposure to selenium has been reported to cause unsteady walking, cyanosis of the mucous membranes, respiratory effects, and gastrointestinal problems, and sometimes results in death. Chronic oral exposure to selenium in humans is principally associated with dermal and neurological effects.

Selenium is an essential nutrient for animals, but excess selenium exposure can induce toxicity. The principal route of selenium exposure in animals is through the diet, and selenium is known to bioaccumulate through the food chain depending on selenium speciation. Selenium toxicity is also dependent on speciation, and the degree of toxicity may be influenced by other factors (for example, water hardness, pH, and sulfate levels).

Instances of CCR releases containing selenium have been reported to adversely affect reproduction and survival of ecological communities. Reduction of CCR releases, ultimately lowering selenium concentrations, resulted in recovery of aquatic communities in some instances. In each of these cases, however, multiple chemicals (for example, other metals in CCPs) were present, and thus not all of the observed effects could be attributed solely to selenium exposure.

Keywords
Coal combustion products
Selenium
Human health
Ecosystem
Ecological health

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1
INTRODUCTION

Sources and Forms of Environmental Selenium

Selenium is a naturally occurring, essential element found throughout the environment. It is found primarily in four valence states (-2, 0, +4, and +6) that form an array of chemical compounds that differ in their solubility, bioavailability, and toxicity. Selenides (-2) include hydrogen selenide, insoluble heavy metal selenides, and organic forms such as dimethyl selenide and dimethyl diselenide, and various selenoamino acids, such as selenomethionine and selenocysteine. Selenomethionine is synthesized in plants and is incorporated randomly in place of methionine in a variety of selenium-containing proteins by animals (including humans), whereas selenocysteine is specifically synthesized in animals and incorporated into animal proteins known as selenoproteins that are involved in essential biological functions (IOM, 2000). Elemental selenium (0) is highly insoluble and is commonly associated with sulfur compounds, such as selenium sulfide (CalEPA, 2001), which is the only selenium compound that is considered a carcinogen. Inorganic selenites (+4), such as selenium dioxide or sodium selenite, and selenates (+6), such as selenic acid and sodium selenate, are the forms most commonly found in soil and water. Due to their solubility, they are readily taken up by plants and converted to organic selenides. Overall, organic forms of selenium are mainly found in grains and other plant products, as well as animal products. Exposure to inorganic selenium (selenites and selenates) occurs mainly from environmental exposures such as soil and drinking water, but inorganic selenium can also be found in plants and some dietary supplements.

Selenium compounds are used in the glass industry as decolorizing agents and in the production of red and black glass (Fishbein, 1983, as cited by ATSDR, 2003). They are also used as accelerators and vulcanizing agents in the rubber industry (Fishbein, 1983, as cited by ATSDR, 2003). Selenium is used in the electronics industry in "electric eyes," photographic exposure meters, photoelectric cells, and rectifiers for home entertainment equipment (ATSDR, 2003). In the past, selenium was used in pesticides, but this use is now restricted (ATSDR, 2003). Selenium dioxide is used to catalyze reactions of organic compounds (CalEPA, 2001). Selenium sulfide is used as an anti-dandruff agent in shampoos and as a constituent of fungicides (ATSDR, 2003). Selenium is intentionally consumed by humans in dietary supplements and is used as a nutritional feed additive for poultry and livestock (IPCS, 1987).

Selenium in Soil

The primary factor controlling selenium concentrations in soil is the selenium content of the parent bedrock that releases selenium through weathering processes and leaching (US FWS, 1985; ATSDR, 2003). Atmospheric deposition from anthropogenic sources such as mining and smelting also contributes to selenium concentrations in soil (Glooschenko and Arafa, 1988, as cited by ATSDR, 2003). The highest natural selenium concentrations in the United States (US) are associated with uranium ores in sandstone-type deposits in the western US, where selenium concentrations as high as 1,000 mg/kg have been found (Shamberger, 1981, as cited by ATSDR, 2003). In accordance with this, the highest US soil levels of selenium are found in the West and Midwest (ATSDR, 2003). The maximum selenium concentration in uncontaminated US soils is reported by the United States Geological Survey (USGS) to be 4.3 mg/kg (Shacklette and Boerngen, 1984), while average background concentrations of total selenium in US soils range from 0.25 to 0.53 mg/kg (Bradley *et al*., 1994; Chen *et al*., 1999; Shacklette and Boerngen, 1984). High soil selenium content has also been observed in other parts of the world. For example, in a region of Western China the average concentration of selenium in soils was 7.9 mg/kg (Yang *et al*., 1983). In this part of China, a stony coal with an unusually high selenium content (averaging 300 mg/kg (up to 80,000 mg/kg) selenium) was identified as the environmental source of selenium-contaminated soils in this region.

The tendency of young children to ingest soil through hand-to-mouth activity is a potential route of exposure that most likely occurs in areas that naturally have high selenium content in the soil. Dermal exposure and inhalation of dust particles from soil surfaces are also possible. The soluble forms of selenium, such as inorganic selenites and selenates, are more likely to be bioavailable in soils than the relatively insoluble selenides or elemental selenium.

Selenium in Water

Selenium is found naturally at low concentrations in surface water and groundwater. Selenium is deposited in surface waters from atmospheric deposition, adjoining waters, surface runoff, subsurface drainage, and effluents from oil, coal, and sewage treatment plants (ATSDR, 2003).

The average concentration of selenium in surface waters in non-seleniferous areas of the US ranges from 0.0001 to 0.0004 mg/L (US EPA, 2004). The selenium concentration in groundwater may reach up to 6 mg/L at locations of unusual geological conditions (Cannon, 1964, as reported in Höberg and Alexander, 1986), but the majority of groundwater samples from seleniferous areas in the US have selenium concentrations an order of magnitude lower (ATSDR, 2003).

In particular, agricultural drainage has led to increased selenium in various water systems (Hoffman, 2002; Ohlendorf, 2002). For example, selenium concentrations in water from 151 wells in the San Joaquin area of California, which has high selenium concentrations because of agricultural and natural processes, were generally below 0.010 mg/L, but had a maximum concentration of 0.272 mg/L (Oster *et al*., 1988, as cited by ATSDR, 2003). The United States

Environmental Protection Agency (US EPA) regulates the amount of selenium in public drinking water supplies, and the concentration is not allowed to exceed 0.05 mg/L of total selenium (as discussed in more detail in the Regulations and Screening Criteria section). The overwhelming majority of drinking water sources tested in the US (*i.e.*, 99.5%) have selenium concentrations less than 0.01 mg/L (Lakin and Davidson, 1967, as cited by ATSDR, 2003).

Another source of selenium release to the environment as a consequence of human activities is from coal fly ash (150,000-460,000 tons of Se are deposited in coal ash per year) that results from coal combustion (ATSDR, 2003). If improperly managed, the selenium present in coal fly ash settling ponds may leach and contaminate nearby surface and groundwater supplies (ATSDR, 2003). Coal power generation operations have also been reported to discharge selenium to surface water bodies in effluents (ATSDR, 2003). For example, Lemly (1985) reported a facility in North Carolina discharged selenium in effluents (0.1 to 0.2 mg Se/L) to a neighboring lake, which caused lake concentrations to reach average levels of 0.01 mg Se/L.

Selenium in Air

Natural sources of selenium in air include volcanic gas and volatilization of selenium by soil microbes, plants, and animals (ATSDR, 2003). The background ambient air concentrations of selenium in the US range from 0.1 to 10 ng/m^3 (Zoller and Reasmer, 1976, as cited by IPCS, 1987).

Selenium in the Diet

The primary route of exposure to selenium in the US is through food consumption. Selenium is found in most foods and is localized mainly in the protein fraction of plant and animal tissues (IPCS, 1987). Among all foods, meat products generally contain the highest concentrations of selenium (0.3 μg/g), while vegetables and fruits contain lower amounts (< 0.01 μg/g; Höberg and Alexander, 1986). Generally, foodstuffs grown in highly seleniferous areas (*e.g.*, Andes Mountains Region; Brazil; Venezuela) will contain much higher levels of selenium than food grown in low selenium areas (*e.g.*, Scandinavia, New Zealand; Höberg and Alexander, 1986). The average intake of selenium per person in the US ranges from 0.071 to 0.152 mg/day (ATSDR, 2003). Selenium is also a required nutrient with a Recommended Daily Allowance of 0.055 mg/day for male and female adults (approximately 0.8 μg/kg/day) (IOM, 2000). This intake is usually achieved through a normal diet, particularly in the US (ATSDR, 2003). Organic forms of selenium, mainly the selenoamino acids, selenomethionine and selenocysteine, make up the greatest portion of selenium intake from foods (ATSDR, 2003). The main inorganic sources of selenium in foods are selenate and selenite, which are less absorbed by the body than organic forms (ATSDR, 2003).

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HUMAN HEALTH EFFECTS AND RISK ASSESSMENT

In terms of human exposure, both organic and inorganic forms of selenium can be ingested from various sources such as food, dietary supplements, drinking water, and soil. A substantial amount of research is available on the health effects associated with selenium ingestion. As described in more detail below, some amount of selenium is required for good health in humans (*i.e.*, selenium is essential), while high selenium exposures are associated with adverse health effects. The essentiality of selenium relates to its functionality in selenoproteins, which contain selenocysteine. Selenoproteins are essential for such processes as thyroid hormone regulation and defense against oxidative stress. The essential *vs*. toxic nature of selenium varies according to the form of selenium, an individual's baseline selenium status, and the level of exposure. The most relevant selenium species for understanding both the beneficial and toxicological effects of selenium ingestion in humans are the various organic selenium compounds as well as inorganic sodium selenite and sodium selenate (Velazquez and Poirier, 1994). The analysis below focuses on these forms of selenium.

Selenium Uptake, Metabolism, and Excretion in the Human Body

Both selenomethionine and selenate are well-absorbed by the GI tract (> 90%) (IOM, 2000), but more selenate is lost in the urine without being incorporated into tissues. The absorption of selenite appears to be more variable, but some human studies have shown that absorption of sodium selenite exceeds 80% (Thomson, 1974, Thomson and Stewart, 1974, Thomson *et al*., 1977, all as cited by ATSDR, 2003; Griffiths *et al*., 1976) and that selenite is retained in the body more than selenate (IOM, 2000).

The absorption of selenium in the respiratory tract is not well-studied, but high urinary selenium levels in workers occupationally exposed to airborne selenium indicate possible pulmonary absorption (ATSDR, 2003). Evidence for dermal absorption of selenium compounds is also limited. There is no evidence that selenate or selenite can be absorbed through the skin in humans or animals, and a single study in mice demonstrated that topically applied selenomethionine was able to penetrate skin (ATSDR, 2003).

Selenium is found in all tissues of the body, and its distribution is relatively independent of the chemical form. Skeletal muscle is the tissue that retains the greatest amount of selenium and accounts for half of the total body selenium, but organs such as the kidneys, liver, and testes have higher relative concentrations of selenium (Navarro-Alarcon and Cabrera-Vique, 2008). Schroeder *et al*. (1970) reported the following order for selenium concentrations in human organs: kidney > liver > spleen > pancreas > testes > heart muscle > intestine > lung > brain.

Selenium is metabolized through a multi-step process. When ingested, inorganic selenium is metabolized to the intermediate hydrogen selenide. The selenide may be converted to a selenophosphate compound that can be incorporated into selenoproteins (*e.g.*, glutathione peroxidase, thyroxine reductase, and iodothyronine) or into transfer ribonucleic acid (tRNA) encoding selenocysteine. Alternatively, the selenide may be methylated and excreted into urine (Lobinski *et al*., 2000). Organic forms of selenium found in plants or animal products are sometimes nonspecifically incorporated into tissues such as skeletal muscle, liver, pancreas, stomach, GI mucosa, and erythrocytes (Schrauzer, 2000, as cited by ATSDR, 2003). Otherwise, organic forms of selenium can have the same metabolic fate as inorganic selenium via conversion to the selenide intermediate (IOM, 2000).

The routes of elimination for selenium are urine, feces, and exhaled breath. Selenium excretion appears to be dose-dependent and related to existing reserves of selenium within the body. In fact, excretion appears to be a key function in selenium homeostasis, as higher selenium intakes result in a higher percentage of selenium excretion (ATSDR, 2003). Inorganic selenium metabolism consists of an initial rapid phase with a half-life of approximately one day, an intermediate phase characterized by a half-life of approximately eight to nine days, and an elimination process with a half-life of 115-116 days (Thomas and Stewart, 1974, as cited by ATSDR, 2003). Selenomethionine has a similar tri-phasic excretion pattern, but the final excretion phase is prolonged, with a half-life of about 207-290 days (Griffiths *et al*., 1976). At high levels of exposure, selenium can be excreted in exhaled breath (Weissman *et al*., 1983; Olson *et al*., 1963, as cited by ATSDR, 2003), but very little selenium is excreted in sweat (Levander *et al*., 1981).

Selenium Measurement in Humans

Total selenium levels in the human body range from 10 to 20 mg (Navarro-Alarcon and Cabrera-Vique, 2008). Selenium can be detected in blood, feces, urine, hair, and nails of exposed individuals at levels that will vary based on dietary habits. Most epidemiological studies have primarily used blood or urine levels to indicate the degree of selenium exposure (ATSDR, 2003). In general, urinary excretion rates of 20 to 200 μg selenium/day are considered normal, and are not associated with either deficiency or toxicity (Sanz Alaejos and Diaz Romero, 1993). When measured in 2003-2004, mean selenium blood serum concentration in the US was 137.1 μg/L (Laclaustra et al., 2009). Selenium in the blood is highly correlated to levels of selenium in regional soils (IPCS, 1987).

Selenium Health Effects

Selenium has been recognized as a potential occupational hazard since the 1920s when the classic marker of selenium toxicity, a garlic odor on the breath, as well as other reported symptoms such as GI disturbances, upper airway irritation, metallic taste, and odor-detecting problems were published in standard industrial health reference books (Hamilton, 1925; Alderman and Bergin, 1986). Since then, it has been recognized that while high doses of selenium can cause adverse health effects, lower doses may be associated with better health and

are, in fact, essential to prevent certain diseases (Figure 2-1). The sections below provide a discussion of the essentiality of selenium, the health benefits associated with selenium supplementation, and the adverse health effects observed at higher doses. Because of the voluminous material available on the health effects associated with selenium ingestion (particularly the health benefits), this review is focused on the effects of environmental exposures to selenium (*i.e.*, in the diet, water, and soil). The review of potential adverse effects is comprehensive, based on the literature to date. Conversely, only an overview of the documented health benefits of selenium is provided. Although environmental exposures are the focus, key experimental selenium supplementation studies are also discussed, particularly those in which adverse effects were studied or were incidentally observed in the context of broader health studies.

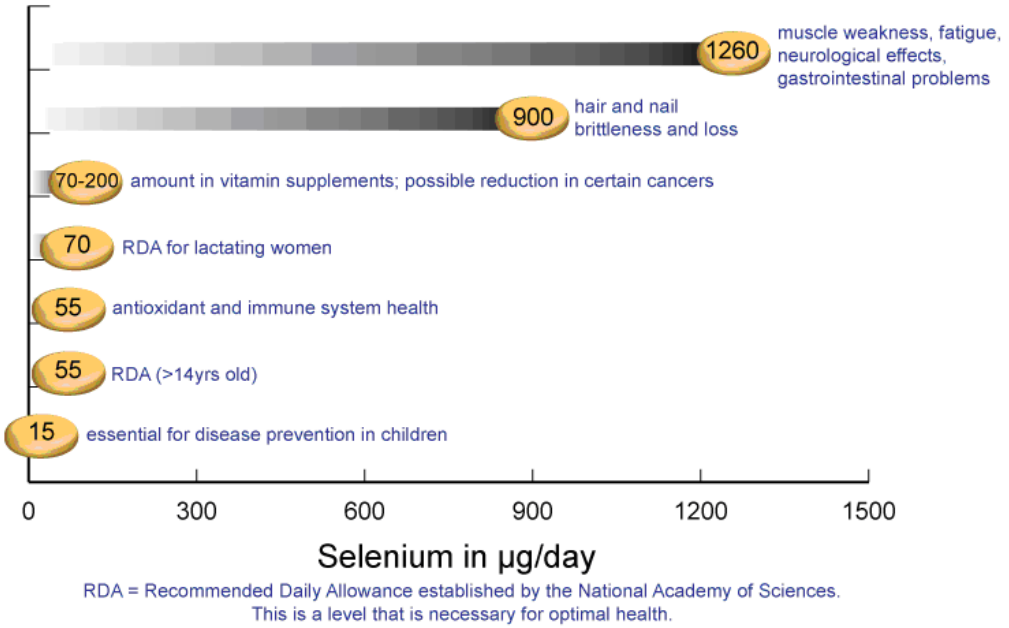

Figure 2-1
Biological Effects of Selenium Ingestion Depend on Dose

Essentiality and Health Benefits of Selenium

Selenium is an essential nutrient for humans and other animals; it is required for normal function, growth, and reproduction (Fan and Kizer, 1990). Selenium functions largely through the modification and expression of at least 30 selenoproteins (Stadtman, 1991, as cited by IOM, 2000; Beckett and Arthur, 2005) with essential biological functions (Van Cauwenbergh *et al.*, 2004, as cited by Navarro-Alarcon and Cabrera-Vique, 2008) (see Table 2-1). Well-characterized selenoproteins include the glutathione peroxidase (GPx), thioredoxin reductase (TR), and iodothyronine deiodinase (IDI) families. These selenoenzymes modify cell function by acting as antioxidants, modifying the redox status of certain molecules, and regulating thyroid hormone metabolism (IOM, 2000). Selenium is essential for optimal endocrine, immune, and testicular function and for moderating the inflammatory response (Hill *et al.*, 2003, McKenzie *et*

al., 2002b, Arthur *et al*., 2003, all as cited by Beckett and Arthur, 2005; Van Cauwenbergh *et al*., 2004, as cited by Navarro-Alarcon and Cabrera-Vique, 2008).

Selenium is a cofactor of the glutathione peroxidase (GPx) family of antioxidant enzymes that are important molecules in the protection against oxidative stress (Navarro-Alarcon and López-Martínez, 2000, Van Cauwenbergh *et al*., 2004, Hartikainen, 2005, Navarro-Alarcon *et al*., 2005, all as cited by Navarro-Alarcon and Cabrera-Vique, 2008). The antioxidative function of selenium can also help to ameliorate ultraviolet radiation-induced damage (Navarro-Alarcon and Cabrera-Vique, 2008).

Selenium has a number of roles in thyroid hormone synthesis, including the conversion of the hormone tetraiodine thyroxin (T_4) to the biologically active triiodine thyroxin (T_3) (Table 2-1; Navarro-Alarcon and Cabrera-Vique, 2008). High dietary intake of selenium is associated with diminished T_3 levels (Goldhaber, 2003, as cited by Navarro-Alarcon and Cabrera-Vique, 2008), whereas low intake is associated with impaired peripheral conversion of T_4 to T_3 (Duffield *et al*., 1999, as cited by Anon., 2003).

Table 2-1
Significant Mammalian Selenoproteins and Their Corresponding Biological Function

Selenoproteins	Biological Function
Glutathione peroxidases	Protection against oxidative stress by scavenging free radicals generated in the body
Iodothyronine deiodinases (multiple forms)	Synthesis and metabolic regulation of thyroid hormones (T_3, T_4, and T_2)
Thioredoxin reductases (multiple forms)	Participates in the reduction of nucleotides in DNA synthesis as well as in the regulation of DNA transcription factors; may be involved in anti-cancer activity
Selenoprotein P	Protection of vascular endothelial cells against oxidative damage
Selenoprotein W	Unknown, but necessary for muscle function
Selenophosphate synthetase (two isoforms)	Biosynthesis of selenophosphate and, consequently, of S-Cysteine, which is necessary for selenoprotein synthesis
Mitochondrial capsule selenoprotein	Shielding of developing sperm cells from oxidative damage
Prostate epithelial selenoprotein	Similar to glutathione peroxidase
DNA-bound spermatid selenoprotein	Similar to glutathione peroxidase
18 kDa selenoprotein	Essential selenoprotein preserved in selenium deficiency

Several specific diseases have been associated with selenium deficiency. The most well-established link is for Keshan disease, a cardiomyopathy in children characterized by cardiac

muscle degeneration (IOM, 2000). Associations with Kashin-Beck Disease, which is a bone and joint disorder, and Myxedematous Endemic Cretinism, which results in mental retardation, have also been reported (NIH, 2009).

The Recommended Dietary Allowance (RDA) for selenium in children is based on criteria for preventing Keshan disease. Adult RDAs are based on selenium levels associated with maximizing plasma GPx activity, which provides protection against oxidative damage (IOM, 2000). The RDA for children 1-18 years of age ranges from 20 to 55 μg/day (depending on the age of the child). For men and women 19 to > 70 years of age, the RDA is 55 μg/day (IOM, 2000). The RDA is 60 μg/day during pregnancy and 70 μg/day during lactation (IOM, 2000).

Beneficial Effects and Associated Doses

There is a vast amount of research on the health benefits associated with selenium exposure. Describing this research in detail is beyond the scope of this document. Below is a summary of some of the overall conclusions from available studies, with more specific information on key recent studies that contribute to the state-of-the-art information on the potential health benefits of selenium.

Overall, epidemiological studies conducted in the last 50 years suggest an inverse relationship between selenium intake and cancer mortality (Anon., 2003). The anti-cancer properties of selenium appear to operate at intakes of about 200 μg/day (Beckett and Arthur, 2005). The connection between selenium and cancer was originally demonstrated by studies relating selenium levels in crops to cancer mortality rates and by studies linking increased cancer risk with low blood selenium levels (Schrauzer and Ishmael, 1974, Shamberger, 1976, Schrauzer *et al*., 1976, Shamberger and Willis, 1971, Jansson *et al.,* 1977, Yang *et al.,* 1983, all as cited by US EPA, 2002a). Since then, many other ecological and prospective studies have also shown a correlation between living in a geographic area with low selenium and increased cancer risk and, conversely, individuals in a population with higher selenium intake from food and lower cancer risk (el-Bayoumy *et al*., 1995, Nomura *et al*., 2000, both as cited by Anon., 2003). Examples of studies reporting a relationship between environmental selenium and better health are summarized below in Table 2-2. It should be noted, however, that there are many more studies than those presented below.

Table 2-2
Summary of Studies on Environmental or Dietary Selenium Exposure Associated With Beneficial Effects

Reference	Study Location	Exposure Metric	Key Results
Shamberger and Frost (1969)	Canada	Foliage plants	Human cancer death rate (all types) in provinces with selenium-containing plants was 122.2 +/- 7.8, while provinces devoid of selenium plants had corresponding death rates of 139.9.
Shamberger and Willis (1971, as cited by US EPA, 2002a)	California	Forage crops	Correlation between decreased cancer death rates (all types) and increased selenium levels in crops.
Vinceti *et al*. (1994)	Northern Italy	Drinking water	No significant difference in the temporal distribution of stroke deaths was observed. Study suggests a beneficial effect of selenium supplementation on coronary disease mortality.
Kellen *et al*. (2006)	Belgium	Serum	Study suggests an inverse association between serum selenium concentration and bladder cancer risk.
Peters *et al*. (2006)	10 States in the US	Serum	Risks for advanced colorectal adenoma were reduced by 26% for each 50 ng/mL increase in serum selenium.
Bleys *et al*. (2008a)	United States	Serum	No association between serum selenium levels and cardiovascular mortality was found. An inverse association was observed with all-cause and cancer mortality at low selenium levels, with a modest increase in mortality at high selenium levels.
Connelly-Frost *et al*. (2009)	North Carolina	Serum	High levels of serum selenium and reported folate status were jointly associated with a substantially reduced risk of colon cancer.
van der Pols *et al*. (2009)	Australia	Serum	High serum selenium concentrations were associated with a 60% decrease in subsequent tumor incidence of skin cancer.

Trumbo (2005) conducted a United States Food and Drug Administration (US FDA) review of the evidence for an association between selenium and cancer and concluded that some evidence permits a qualified health claim. The most consistent evidence was noted for breast and prostate cancers (Trumbo, 2005). Silvera and Rohan (2007, as cited by Navarro-Alarcon and Cabrera-Vique, 2008) also reported evidence of an inverse relationship between selenium exposure and prostate cancer risk, and possibly a reduction in risk with respect to lung cancer. The Nutritional Prevention of Cancer Trial, a randomized clinical study designed to evaluate the efficacy of 200 μg/day selenium (in the form of selenized yeast) in preventing the recurrence of non-melanoma skin cancers among 1,312 residents of the eastern US, showed striking inverse relationships between treatment and the incidence of total, lung, prostate, and colorectal cancer, as well as total cancer mortality (Clark *et al*., 1996). Interestingly, a more recent clinical trial specifically designed to evaluate the relationship between selenium supplementation and prostate cancer did not find that selenium affected prostate cancer risk (Lippman *et al*., 2009). Other health endpoints assessed (*e.g.*, colorectal and lung cancer, all other primary cancers, cardiovascular disease) also showed no reduction in incidence or mortality with selenium supplementation. This study involved over 35,000 men (with almost 9,000 in the selenium treatment group) who were followed for a mean of 5.46 years.

There is some evidence that selenium status may influence various non-cancer diseases. An inverse correlation exists between the appearance of certain cardiac diseases and low selenium levels in the environment, diet, and blood (Navarro-Alarcon and López-Martínez, 2000, as cited by Navarro-Alarcon and Cabrera-Vique, 2008). Flores-Mateo *et al*. (2006) performed a meta-analysis of 25 observational studies that examined the relationship between selenium and coronary heart disease and found that higher selenium exposure was associated with a lower coronary heart disease risk. The authors report that despite this observation, there is no conclusive evidence that selenium supplementation will decrease cardiovascular disease risk (Flores-Mateo *et al*., 2006).

Multiple studies have suggested that the intake of selenium through supplementation has immune-enhancing properties. For example, selenium supplementation increased B and T lymphocyte proliferative ability (Hawkes *et al*., 2001; Peretz *et al*., 1991), natural killer (NK) cell activity, cytotoxic lymphocyte-mediated tumor cytotoxicity (Kiremidjian-Schumacher *et al*., 1994, as cited by ATSDR, 2003), and the killing of bacteria by leukocytes (Arvilommi *et al*., 1983). These functional changes in immune responses may lead to an increased ability to fight infections. Because of its modulatory effects on the immune system, selenium may help slow or minimize the effects of HIV infection (NIH, 2009). For example, a study by Baum *et al*. (1997, as cited by Anon., 2003) found that HIV patients with low plasma selenium (< 85 μg/L) had a greater risk of mortality than those with adequate levels of selenium.

Antagonistic Effects of Selenium

There is some evidence that selenium protects humans and animals against toxicity associated with high exposures to heavy metals such as arsenic, mercury, lead, cadmium, and silver (Levander and Burk, 1994, Caurant *et al.*, 1996, Thorne, 2003, Navarro-Alarcon *et al.*, 2005,

Cabañero *et al.*, 2007, Mousa *et al.*, 2007, all as cited by Navarro-Alarcon and Cabrera-Vique, 2008; Kibriya *et al*., 2007; Holmberg and Fern, 1969). Selenium has a high affinity for many heavy metals and may exert its protection, in part, by binding to metals and rendering them unavailable for interference with biological processes. Many studies provide evidence for the antagonism of selenium against the toxic effects of arsenic and mercury in particular.

Low blood selenium levels have been associated with a greater risk of skin lesions in populations exposed to elevated levels of arsenic in drinking water in Bangladesh (Chen *et al*., 2007) and China (Huang *et al*., 2008). In a Swedish case-control study of copper smelter workers exposed to arsenic and other metals (Gerhardsson *et al*., 1985), low selenium concentrations in lung tissue were associated with lung cancer deaths. Human studies in which selenium supplementation was used in arsenic-exposed populations to reduce adverse effects have had mixed results (Chen *et al*., 2007). For example, in a pilot study by Verret *et al*. (2005), as cited in Chen *et al*. (2007), selenium supplementation for six months was associated with a small, but not statistically significant, improvement in skin lesions in arsenic-exposed Bangladeshi subjects.

Antagonistic Effects of Selenium with Arsenic

It has long been known that selenium protects against toxicity in animals exposed to arsenic. For example, selenium has been shown to be protective against arsenic-induced birth defects in hamsters (Holmberg and Fern, 1969) and against thyroid toxicity in weanling rats (Glattre *et al*., 1995). Selenium has also been shown to protect against arsenic-induced cancer in animals. In hairless mice, selenium prevented skin tumors due to arsenic exposure with or without concurrent exposure to ultraviolet radiation (Burns *et al*., 2008). In another study, mice given selenium in combination with arsenic had fewer chromosomal aberrations in their bone marrow cells than those given arsenic alone (Biswas *et al*., 1999). Arsenic can also counteract the protective effects of selenium. For example, while selenium prevented the development of mammary tumors in mice infected with the murine mammary tumor virus, the co-administration of arsenic with selenium resulted in tumor formation (Schrauzer, 1987).

There are several proposed modes of action for the protective effects of selenium against arsenic toxicity. The primary interaction is thought to be the formation of a conjugate of selenium and arsenic with glutathione, which renders the arsenic less available for absorption into tissues and more readily excreted in urine and bile (Chen *et al*., 2007; Zeng *et al*., 2005; Burns *et al*., 2008). Other hypothesized modes of action include inhibition of arsenic-induced cell signaling and inhibition of the formation of methylated arsenic metabolites (Zeng *et al*., 2005; Kenyon *et al.*, 1997; Styblo and Thomas, 2001).

Antagonistic Effects of Selenium with Mercury

Many studies conducted in animals and in cell culture systems have shown that selenium can counteract some of the toxic effects of mercury (Mozaffarain, 2009). For humans, however, no study has conclusively shown that selenium can modify the relationship between mercury and specific diseases. Yoshizawa *et al*. (2002) found no associations among mercury, selenium, and

incidence of heart disease in a US population. Two studies conducted in Europe found associations between mercury levels and heart disease, but associations with selenium were not measured (Guallar *et al*., 2002; Virtanen *et al*., 2005). Mozaffarian (2009) speculated that in the European studies, associations between mercury and heart disease were apparent because these populations had relatively low selenium intakes, while overall higher selenium intakes in the US protect against mercury-induced heart disease. Further research is needed to confirm any protective effects of selenium against mercury-induced heart disease. No protective effects of selenium on mercury-induced neurotoxicity were observed in three studies of children from high mercury-exposed populations in the Faroe Islands (Choi *et al*., 2008; Steuerwald *et al*., 2000) and Northern Quebec (Saint-Amour *et al*., 2006).

In animals, the protective effects of selenium against the toxicity of both inorganic mercury and methylmercury have been well-established (Goyer, 1997; Khan and Wang, 2009). An early report of selenium protection against methylmercury-induced mortality and weight gain suppression in rats (Ganther *et al*., 1972, as cited by Watanabe, 2002) was followed by several other reports of selenium protection against mercury effects, including neurotoxicity in mice and rats (Satoh *et al*., 1985, Imura, 1986, Watanabe *et al*., 1999a, all as cited by Watanabe, 2002; Fredriksson *et al*., 1993; Glaser *et al*., 2010) and fetal death in mice (Nishikido *et al*., 1987, as cited by Watanabe, 2002). In cell cultures, selenium has also been observed to protect against mercury-induced toxicity. In red blood cell lines, selenium protected against mercury-induced cell death (Frisk *et al*., 2003) and inhibition of enzymes, such as glutathione reductase (Mykkaran and Ganther, 1974, as cited in Skerfving, 1978). Selenium also inhibited methylmercury and ethylmercury toxicity to cultures of rat brain nervous tissue (Kasuya, 1976, as cited by Skerfving, 1978).

The modes of action by which selenium protects against mercury toxicity are unclear. The primary interaction is thought to be the formation of a complex of mercury, selenium, and selenoprotetin P, a selenium-containing plasma protein (Khan and Wang, 2009; Rooney, 2007). The formation of this complex renders the mercury unavailable for interaction with other cell and tissue components, and it is excreted from the body in the urine (Khan and Wang, 2009; Rooney, 2007; Chen *et al*., 2006). It has also been hypothesized that mercury exerts its toxic effects at least in part by complexing with and depleting selenium (Khan and Wang, 2009; Berry and Ralston, 2008; Falnoga and Tusek-Znidaric, 2007). Thus, an abundance of selenium would protect against its depletion by mercury. Other modes of selenium action may include protection against mercury-induced free radical formation by the antioxidative properties of selenium-containing proteins (Khan and Wang, 2009; Chen *et al*., 2006), redistribution of mercury to less-sensitive organs and tissues, and competition for protein binding sites (Cuvin-Aralar and Furness, 1991).

Acute Adverse Health Effects

Acute oral exposure to selenium (*i.e.*, consuming high amounts of selenium over a brief period) has been reported to cause unsteady walking, cyanosis of the mucous membranes, and labored breathing that sometimes results in death (US EPA, 2002a). Lethal or near-lethal doses of

selenium in humans have also been reported to cause respiratory effects such as pulmonary edema and lung lesions; cardiovascular effects such as tachycardia; GI effects including nausea, vomiting, diarrhea, and abdominal pain; liver effects; and neurological effects such as aches, irritability, chills, and tremors (ATSDR, 2003). A condition known as subacute selenosis that results from exposure to large doses of selenium over a long period (weeks) causes neurological dysfunction (impaired vision, ataxia, disorientation, paralysis) and respiratory distress (Alderman and Bergin, 1986; Rosenfeld and Beath, 1964 as cited by US EPA, 2002a; Velazquez and Poirier, 1994). This condition, seen most frequently in livestock that consume selenium-accumulating plants, has been referred to as "blind staggers." Although this condition appears to be related to the ingestion of plants with high selenium content, the clinical features of "blind staggers" have not been replicated in a laboratory setting in which animals were administered high doses of selenium, suggesting other plant compounds may be involved (ATSDR, 2003).

While acute selenosis is infrequently diagnosed in humans, Sutter *et al*. (2008) described a recent clinical case of selenium poisoning in a 55-year-old woman who consumed an improperly formulated selenium supplement (Sutter *et al*., 2008). For several weeks, the patient had been consuming a liquid supplement containing 24 mg of selenium per day, a level over 400 times the recommended daily allowance of 55 μg. The patient experienced six weeks of diarrhea, followed by hair loss two weeks later, as well as fingernail changes (*i.e.*, "Mees" lines). An older report described similar symptoms in an individual who ingested a supplement contaminated with excess selenium (27.3 mg selenium per tablet) over a period of several months (CDC, 1984).

Chronic Non-cancer Adverse Health Effects

Despite the vast amount of information available on the health benefits from chronic exposure to selenium, the information on adverse health effects, particularly from environmental exposures, is limited. In general, chronic oral exposure to selenium in humans is principally associated with dermal and neurological effects. The dermal effects include hair loss, deformation and loss of nails, and discoloration and excessive decay of teeth, while neurological effects include numbness and varying degrees of paralysis (ATSDR, 2003). Effects such as malodorous breath, fatigue, anorexia, gastroenteritis, hepatic degeneration, enlarged spleen, erosion of the joints, anemia, and cardiac atrophy have also been reported at very elevated doses in some studies (Alderman and Bergin, 1986; Harr and Muth, 1972, as cited by US EPA, 2002a; Velazquez and Poirier, 1994; ATSDR, 2003). As described in more detail below, studies from areas in China provide the best information about chronic oral exposure to selenium. While a few additional studies outside the US have also reported a relationship between environmental exposure to selenium and adverse effects, no robust epidemiological study conducted in the US has shown that exposure to selenium in soil, water, or food causes any increased health risks. An association between selenium serum levels and increased diabetes risk has been noted in two recent cross-sectional studies conducted on the US populations (see discussion later in this chapter).

The potential adverse effects of selenium ingestion have also been examined in experimental studies where subjects were administered selenium either in a diet or a supplement. Some of

these studies are shorter-term studies (less than chronic exposure), however, and their relevance to environmental selenium exposures remains to be defined. Results from these key experimental studies are also discussed below and summarized in Table 2-3.

Environmental Exposure Studies Outside the US

Most of what is known about the adverse effects of chronic environmental exposure to selenium comes from a series of studies conducted in the Wudang Mountains in Western China. This area contained high levels of selenium in water, soil, and plants, mainly from the mining and use of coal with a high selenium content (averaging over 300 μg/g selenium) (Yang *et al*., 1983). The mean concentration of selenium in drinking water in this area was 54 μg/L, and the mean soil concentration of selenium was 7.9 mg/kg. The studies in this area focused on a three-year period of severe drought (1961-1964) when the levels of selenium spiked and the estimated dietary intake was even much higher than the population's typical intake (Yang *et al*., 1983; 1989; Yang and Zhou, 1994).

In an initial study, Yang *et al*. (1983) described the health effects observed in this high-selenium area. These included a high prevalence of nail deformities, alopecia, skin lesions, tooth decay, and neurological changes (*e.g.*, paresthesias, hyperreflexia). Additionally, Yang *et al*. (1983) examined selenium levels in the blood, urine, and hair of residents, as well as in crops and soil. Average hair, blood, and urine levels were about 90, 30, and 100 times higher than levels measured in an area with more typical selenium exposures, respectively. Based on the high content of selenium in key crops in the area, Yang *et al*. (1983) estimated the average daily intake to be 5,000 μg/day. In another area of China, also with high environmental exposure to selenium but with no evidence of selenosis in the population, the authors estimated the average daily selenium intake to be 750 μg/day.

Subsequent studies conducted in the same area provided a more quantitative analysis of the selenium exposures associated with adverse effects (Yang *et al*., 1989; Yang and Zhou, 1994). Selenium exposure was estimated using information on the relationship between selenium blood levels and intake. Yang *et al*. (1989) concluded that symptoms of selenosis in susceptible individuals were found at 910 μg/day (or 0.016 mg/kg-day).[1] Changes in certain biochemical endpoints, such as increased prothrombin time, decreased ratio of plasma selenium to selenium in red blood cells, and reduced glutathione serum concentrations, were estimated to occur at slightly lower intakes (~750 μg/day). There was no evidence of any adverse health effects related to the liver, heart, or nervous system, nor was there evidence that selenium exposure caused birth defects (Yang *et al*., 1989). Overall, it was concluded that the daily safe intake of selenium was about 750-850 μg/day (Yang *et al*., 1989).

To further clarify a daily intake of selenium that is likely to be without adverse effects, blood levels and associated clinical effects were re-examined in five individuals from the Yang *et al*. (1989) study (Yang and Zhou, 1994). It was determined that a selenium blood level of 968 μg/L

[1] Assumes a typical Chinese individual weighs 55 kg.

was not associated with any adverse effect, and this blood level corresponded to an intake of 819 μg/day selenium (or 0.015 mg/kg-day), according to the authors' analysis. These studies have been relied upon for the development of non-cancer toxicity criteria for selenium by several different regulatory agencies (as discussed in the Human Health Risk Assessment section).

Several other studies conducted outside the US have examined populations exposed to elevated levels of selenium in the environment. A series of studies conducted in Italy examined the effects on public health of mildly elevated selenium in the water supply (Vinceti *et al*., 1994, 1996, 1998, 2000). Selenium, in the form of selenate, was estimated at 7-9 μg/L, which is above typical levels but still well below the US standard (50 μg/L). There was no evidence of adverse reproductive outcomes associated with selenium exposure, and a beneficial effect of selenium on cardiovascular diseases was suggested (Vinceti *et al*., 1994). One of the studies identified a statistically significant association with amyotrophic lateral sclerosis (ALS) (Vinceti *et al*., 1996) and another with melanoma, as discussed below (Vinceti *et al*., 1998). It should be noted, however, that this series of studies has several serious methodological shortcomings, including a lack of information on baseline selenium status, an insufficient consideration of confounding factors, and poor exposure characterization. Importantly, the elevation of selenium in the water supply was small and, without a more complete exposure assessment, it would be difficult to confirm that selenium intake was significantly higher in the "exposed" population compared to the typical range of dietary levels. Because of the issues with study design, all reported effects in these studies, both beneficial and harmful, should be considered preliminary and they require confirmation.

A study conducted in Venezuela found that children living in a high-selenium region of the country had reduced hemoglobin and hematocrit levels (measures of anemia) compared to children living in a low-selenium area (Jaffe *et al*., 1972, as cited by ATSDR, 2003). This study, however, also found that these same children had a poorer diet, consumed less milk, and had a higher incidence of intestinal parasites, which may explain this difference. Another Venezuelan study in a high-selenium area found that lactating women with higher selenium intake (range 250-980 μg/day) had lower thyroid hormone levels [3,3,5-triiodothyronine (T3), specifically] compared to a similar population with more typical selenium intakes (90-350 μg/day). Although the thyroid hormone levels were statistically significantly decreased, they were still within normal levels. The authors noted that the effect of selenium on thyroid levels was not observed at levels below 350-450 μg/day (Brätter and Negretti De Brätter, 1996, as cited by ATSDR, 2003).

Environmental Exposure Studies in the US

A few studies examining environmental exposure to selenium and potential health effects have been conducted in the US. Longnecker *et al*. (1991) conducted a study in 142 farmers living in highly seleniferous areas of South Dakota and Wyoming. The authors estimated that the selenium intakes in these farmers ranged from 68 to 724 μg/day, with a mean of 239 μg/day. Exposure was assessed by measuring the selenium content in the individual diets of the study participants as well as selenium in whole blood, serum, nails, and urine several times over a two-

year period. The authors did not find any meaningful relationship between selenium exposure (as measured by dietary intake, nail concentration levels, or blood levels) and general measures of blood chemistry and hematology. Notably, no changes in prothrombin time were observed, as in the study of the high seleniferous region in China (Yang *et al*., 1989). The authors also evaluated the incidence of known selenium-related clinical effects (*e.g.*, muscle twitches, paresthesia, nail problems). No clinical signs were associated with selenium exposure after controlling for confounders and eliminating outlier observations.

In another US study, Bednar and Kies (1991) examined the health effects of consuming drinking water with elevated levels of selenium. In an ecological survey of 453 communities in Nebraska, they compared the death rates per 100,000 for heart disease, cancer, cerebrovascular disease, pneumonia, and chronic lung disease in 1986 to levels of inorganic constituents collected from 1986 to 1987. While 42 communities had water samples exceeding the former 100 μg/L state and federal standards for selenium (mean selenium level of 7 μg/L, range < 5 to 130 μg/L), there was no statistically significant relationship between selenium and any of the health effects studied. Bednar and Kies (1991) stated that although their analysis cannot prove or disprove a cause and effect relationship, the results suggest that there are no immediate health risks from selenium at the levels found in the Nebraska drinking water.

The lack of associations between high environmental exposure to selenium and adverse health effects in the US has been hypothesized to be attributable to the lower doses of selenium experienced in US populations compared to the Chinese and Venezuelan populations. In addition, American diets contain more protein, methionine, zinc, vitamin E, and dietary sulfates relative to the Chinese diet, and these all act to reduce selenium toxicity (Wilber, 1980, Fan *et al*., 1988, both as cited by IPCS, 2001; Jonnalagadda and Rao, 1993; Barceloux, 1999).

The National Health and Nutrition Examination Survey (NHANES) is a health survey that examines a nationally representative sample of about 5,000 persons each year for various indicators of environmental exposures, nutritional status, and health endpoints. Based on these data, evaluations of the relationship between environmental exposures and health endpoints are selectively and periodically published. Using the data available from 1988-1994 for 10,478 adults, Bleys *et al*. (2007) reported a relationship between the highest selenium serum concentrations (137.66 ng/L) and diabetes incidence [odds ratio: 1.57 (1.16 to 2.13)]. There was no dose-response relationship, however. An analysis of more recent serum data from NHANES (2003-2004) showed a consistent dose-response relationship between serum selenium and diabetes incidence. At the highest exposure category (> 147 μg/L), the odds ratio was 7.64 (3.34 to 17.46) (Laclaustra *et al*., 2009). Overall serum selenium levels were higher in this more recent survey compared to the 1988-1994 data, perhaps partly due to the expanded use of dietary supplements.

Other recent NHANES evaluations have examined additional health endpoints. Based on the 1988-1994 NHANES data, Bleys *et al*. (2008b) determined that there was a relationship between selenium exposure and various measures of serum lipid levels (*e.g.*, cholesterol). An evaluation of the same NHANES data, however, did not indicate that selenium levels were associated with an increased risk of dying from cardiovascular disease. This study also showed that overall

mortality (and cancer mortality in particular) was decreased with serum selenium concentration (Bleys *et al*., 2008a). An evaluation of the more recent data (2003-2004) did not establish a relationship between selenium status and peripheral artery disease (Bleys *et al*., 2009).

It should be noted that while the evaluation of NHANES data provides a useful way to examine potential adverse (and beneficial) effects associated with selenium exposure in the US population, no causal connections between selenium and health effects should be inferred from these studies. Most of these studies are cross-sectional, meaning that exposure and disease were evaluated at the same point in time, examining selenium levels in people who already have (or do not have) the disease in question. If selenium did cause the disease, the effect would be due to exposures in the past, and current "snapshot" measurements, well after the fact, cannot reliably determine the levels of exposure at the earlier times in which any disease causation occurred.

It should also be noted that some additional observational studies indicating adverse effects from selenium in the US do exist (summarized in Table 2-3). Some of these studies are over 50 years old and have significant methodological flaws that limit their ability to draw any conclusions about exposure to environmental selenium and adverse health effects. Despite the limitations of these studies, there are very few studies that have evaluated the relationship between environmental selenium and health effects in the US, so these studies are included in Table 2-3 for completeness.

Table 2-3
Summary of Studies Evaluating the Association between Environmental or Dietary Selenium Exposure and Adverse Effects

Reference	Study Location	Exposure Metric	Results
Kellen *et al*. (2006)	Belgium	Serum	Study suggests an inverse association between serum selenium concentration and bladder cancer risk
Jaffe *et al*. (1972, as cited by ATSDR, 2003)	Venezuela	Drinking water	Reduced hemoglobin and hematocrit levels associated with selenium levels
Yang *et al*. (1983)	Western China	Dietary intake, hair, blood, urine, water, and soil	High prevalence of selenosis (nail deformities, alopecia, skin lesions, tooth decay, and neurological changes) with higher selenium intakes
Yang *et al*. (1989)	Western China	Dietary intake, blood	Selenosis observed in individuals at 910 µg/day (or 0.016 mg/kg-day). Selenium intake of 400 g is suggested as the maximum daily safe intake.

Table 2-3 (continued)
Summary of Studies Evaluating the Association between Environmental or Dietary Selenium Exposure and Adverse Effects

Reference	Study Location	Exposure Metric	Results
Brätter *et al*. (1991, as cited by ATSDR, 2003)	Venezuela	Blood, hair, breast milk	A significant decrease in height was suggested for children from a high selenium area.
Vinceti *et al*. (1996)	Northern Italy	Drinking water	Sporadic Amyotrophic Lateral Sclerosis (ALS) diagnoses were confirmed in four cohort members with the longest ascertainable period of exposure.
Brätter and Negretti De Brätter (1996, as cited by ATSDR, 2003)	Venezuela	Blood, toenails, breast milk	Lower thyroid hormone levels (T3) with higher selenium levels, but still within normal limits. Effects were significant at selenium intake levels of 350-450 µg/day.
Vinceti *et al*. (1998)	Northern Italy	Drinking water	Melanoma incidence was 3.9 times greater in the selenium-exposed cohort.
Vinceti *et al*. (2000)	Northern Italy	Drinking water	Rates of spontaneous abortions were increased slightly compared to rates among unexposed women from the same municipality.
Hira *et al*. (2004)	India	Dietary intake, hair, urine, fingernails	Selenium content in hair, nails, and urine was high. Loss of hair and blackening/loss of nails were observed. Mean dietary selenium intake exceeded 600 µg/day.
Yang and Zhou (1994)	Western China	Dietary intake, blood	A selenium blood level of 968 µg/L (or 0.015 mg/kg-day) was not associated with any adverse effects.

Table 2-3 (continued)
Summary of Studies Evaluating the Association between Environmental or Dietary Selenium Exposure and Adverse Effects

Reference	Study Location	Exposure Metric	Results
Bleys *et al*. (2008b)	United States	Serum	No association between serum selenium levels and cardiovascular mortality. An inverse association was observed with all-cause and cancer mortality at low selenium levels, with a modest increase in mortality at high selenium levels.
Bleys *et al*. (2009)	United States	Serum	No significant association between serum selenium levels and the prevalence of peripheral arterial disease.
Bleys *et al*. (2007)	United States	Serum	High serum selenium levels were positively associated with the prevalence of diabetes.
Bleys *et al*. (2008a)	United States	Serum	Highest quartile of serum selenium had 10% higher triacylglycerols than participants in the lowest quartile.
Laclaustra *et al*. (2009)	United States	Serum	High serum selenium concentrations were associated with slightly higher prevalence of diabetes, higher fasting plasma glucose, and glycosylated hemoglobin levels.
Smith *et al*. (1936, as cited by ATSDR, 2003)	North Central US	Urine	No adverse effects associated with urine selenium levels in 111 families affected with "Alkali Disease" symptoms that were suspected to be from selenium poisoning.
Smith and Westfall (1937)	North Central US	Dietary intake, drinking water, urine	None of the adverse health effects observed in 76% of a cohort with "Alkali Disease" can be ascribed to selenium exposure.
Howe (1979, as cited by ATSDR, 2003)	South Dakota	Blood, urine, hair	Chronic toxicolosis from selenium could not be stated from this study.

Table 2-3 (continued)
Summary of Studies Evaluating the Association between Environmental or Dietary Selenium Exposure and Adverse Effects

Reference	Study Location	Exposure Metric	Results
Longnecker *et al.* (1991)	North Central US	Dietary intake, blood, toenails, urine	No relationship between higher than average selenium exposure (*i.e.*, 54% higher than 19 US cities) and adverse health effects.
Bednar and Kies (1991)	Nebraska	Drinking water	Levels of selenium exceeded the former Nebraska Department of Health standard for drinking water (0.01 mg/L) in 42 communities but were not significantly correlated with any adverse health effects.

Experimental Supplementation Studies

Several studies have experimentally examined potential health effects associated with selenium supplementation or a high-selenium diet. Hawkes and Turek (2001) administered 11 healthy men a diet consisting of 47 μg/day selenium for 21 days. On day 22, the group was divided in half, with one group receiving 13 μg/day and the other 297 μg/day selenium in their diet. Both the high and low selenium diet were associated with a statistically significant decrease in sperm concentration and total sperm number. Sperm motility was also reduced in the high-selenium group, but the change was not consistent over the course of the study and was only slightly below the normal levels. No changes in levels of testosterone or other hormones were noted. A follow-up to this study, with a greater number of subjects and a more robust methodological design, found that selenium had no effect on the selenium content of sperm, serum androgen concentrations, sperm count, motility, progressive velocity, or morphology (Hawkes *et al*., 2009). The 2001 study also evaluated immune function in study participants (but presented this information in a separate publication). The study found that selenium enhanced, not impaired, immune function (Hawkes *et al*., 2001).

In 2003, the same group published results related to thyroid function. Some changes in thyroid hormone levels (T3) were observed in the high and low dose selenium groups (T3 increased in the low selenium group and decreased in the high selenium group). The level of T3 at the end of the study was still well within levels typically found within the general population. Although the toxicological significance of the decreased T3 levels is uncertain, the result is consistent with the Venezuelan study described above. The authors also noted that the decreased thyroid hormone levels in the higher dose selenium group were associated with a slight, but statistically significant, weight gain (73.5 kg at baseline and 74.2 kg at the end of the 120-day study).

Some experimental selenium supplementation studies have noted adverse effects in the context of evaluating selenium's health benefits. In 2007, Stranges *et al.* (2007) re-examined results

from the Nutritional Prevention of Cancer trial, which, as explained in the "Health Benefits" section, was a clinical study designed to examine the effect of selenium supplementation on skin cancer. Stranges *et al.* (2007) used relevant data from the study to evaluate the relationship between selenium and diabetes. They found a small, but statistically significant, association [hazard ratio: 1.55 (95% CI 1.03-2.33)]. When analyzed by baseline serum selenium level, only the group with highest baseline serum selenium level (> 121 μg/L) showed an increase in diabetes risk (Stranges *et al*., 2007).

A more recent clinical trial designed to examine the beneficial effects of selenium on prostate cancer also evaluated some secondary health endpoints. This study, called the Selenium and Vitamin E Cancer Prevention Trial (SELECT), began in 2001 and involved 35,533 men aged 50 to 55 years. Four groups were studied and the groups were treated with either selenium only (200 μg/day L-selenomethionine), Vitamin E only (400 IU/day), both selenium and Vitamin E, or a placebo. After about 5.5 years of follow-up, a safety monitoring committee met in September 2008 and decided to discontinue the study prematurely based on a lack of benefit from either agent in reducing prostate cancer risk. This study also examined the relationship between diabetes and selenium intake, and reported that the increase in diabetes was not statistically significant (Lippman *et al*., 2009). This finding is consistent with a large clinical trial conducted in France that observed no relationship between selenium supplementation (100 μg/day) and fasting blood glucose (Czernichow *et al*., 2006).

Cancer Health Effects

In both human and animal studies, there is no convincing evidence that exposure to environmental selenium is associated with an increase in cancer. In fact, there is strong evidence that populations with diets deficient in selenium may have a higher cancer risk than populations with sufficient selenium in their diet (Schrauzer and Ishmael, 1974, Shamberger, 1976, Schrauzer *et al*., 1976, Shamberger and Willis, 1971, Jansson *et al.,* 1977, Yang *et al.,* 1983, all as cited by US EPA, 2002a) (see Table 2-2). The relationship between selenium supplementation and cancer prevention is more complicated and under active investigation. Overall, there appears to be some cancer health benefit for supplementation in individuals with a low selenium status, but supplementation in selenium-sufficient individuals offers limited benefit. Selenium has also been found to have chemopreventive qualities for people with existing tumors (ATSDR, 2003).

Studies reporting a relationship between selenium ingestion and increased cancer risk are limited.[2] An Italian research team studied the effect of a selenium-contaminated water supply on melanoma incidence in the exposed population of 2,065 individuals (Vinceti *et al*., 1998). While an association was identified, this study had several methodological shortcomings, including inadequate exposure assessment and lack of correction for confounding factors. Other studies with a much more robust scientific design reported no association between selenium intake and melanoma (Clark and Alberts, 1995), including a recent large study that examined selenium

[2] In our research, we located only one study reporting a positive relationship between selenium and cancer. While our research was comprehensive, it was not exhaustive.

intake from supplements in over 69,000 study participants over a 10-year period (Asgari *et al*., 2009).

Thus, there is overwhelming evidence that selenium exposure, at least, is not associated with any adverse cancer outcome, and at best, can help or prevent cancer under some circumstances. Some of the data on the relationship between selenium ingestion and reduced cancer risk has already been discussed throughout this report (see Table 2-2).

In animal studies (rodents, specifically), selenium sulfide and ethyl selenac (selenium diethyldithiocarbamate) administered orally are the only selenium species that have been shown to be carcinogenic (Innes *et al*., 1969; NCI, 1968, as cited by ATSDR, 2003). Human exposure to these species of selenium compounds is extremely unlikely (ATSDR, 2003). Overall, animal studies that have evaluated sodium selenate, sodium selenite, or organic forms of selenium have reported negative results for the development of cancer (as reviewed by ATSDR, 2003). While some older studies have reported increases in certain types of cancers in long-term animal studies, these studies have several methodological flaws including inadequate pathological evaluations, inappropriate or non-existent statistical analysis, lack of a control group, and the presence of viral infections in some of the animals (ATSDR, 2003). Newer, more well-conducted long-term animal studies fail to find a reliable association between selenium exposure and increased tumor incidence (ATSDR, 2003).

Selenium Human Health Risk Assessment

Non-cancer and cancer toxicity data are used to develop chemical-specific toxicity factors, and these are used to quantitatively evaluate human health risks. Reference Doses (RfDs) are used to assess non-cancer risks, and cancer slope factors (CSFs) are usually used to evaluate cancer risks. All US EPA-derived toxicity factors are published on the Integrated Risk Information System (IRIS). The IRIS database serves as an important resource because it allows scientists to standardize the risk assessment process by using a common set of toxicity criteria.

Evaluation of Non-cancer Risks

As defined by US EPA, an RfD is intended to represent a level of daily human exposure, experienced over the course of a lifetime, which is likely to be without an appreciable risk of deleterious effects, even for susceptible members of the population (US EPA, 1993). For non-cancer risks, a threshold for chemical toxicity is typically assumed (*i.e.*, there is a dose below which adverse health effects are not observed). To derive an RfD, the chemical-specific threshold dose must be defined. This is accomplished by identification of a Lowest Observed Adverse Effect Level (LOAEL) and/or a No Observed Adverse Effect Level (NOAEL), from either human epidemiological or laboratory animal toxicology studies. After determining the NOAEL or LOAEL, this dose is divided by uncertainty factors (UFs) to account for potential uncertainties (including inter- and intra-species differences in sensitivity, insufficient study durations, use of a LOAEL instead of a NOAEL, and data deficiencies) to arrive at a final RfD. The application of UFs in the derivation of the RfD helps ensure that the RfD is health-

protective. It should be noted, however, that, according to the US EPA, "it should not be categorically concluded that all doses below the RfD are 'acceptable' (or will be risk-free) and that all doses in excess of the RfD are 'unacceptable' (or will result in adverse effects)" (US EPA, 1993).

Derivation of the US EPA Oral RfD for Selenium

US EPA (2002a) has derived an oral RfD for selenium compounds, based on a study of a population living in an area of China with unusually high environmental concentrations of selenium (Yang *et al*., 1989) (described in an earlier section). Among the population, the study authors reported apparent dose-related increases in the incidence of the characteristic "garlic odor" of excess selenium excretion in the breath and urine, thickened and brittle nails, hair and nail loss, lowered hemoglobin levels, mottled teeth, skin lesions, and central nervous system (CNS) abnormalities (peripheral anesthesia, acroparesthesia, and pain in the extremities). Following an examination of the blood selenium levels to determine clinical signs of selenium intoxication, a whole blood selenium concentration of 1.35 mg/L and a selenium intake of 1.261 mg/day was determined as the lowest selenium intake associated with overt signs of toxicity. The next lowest whole blood selenium concentration of 1.0 mg/L, which corresponded to an intake of 0.853 mg selenium/day, or 0.015 mg/kg-day, was not associated with adverse effects. US EPA used this value as the NOAEL to derive the RfD (US EPA, 2002a). This NOAEL was divided by a UF of 3 (to account for sensitive individuals), resulting in a chronic oral RfD for selenium of 0.005 mg/kg-day (ATSDR, 2003; US EPA, 2002a). It should be noted that, given the uncertainty factor incorporated into the RfD calculation, selenium risks estimated in a risk assessment are conservative, and likely overestimate human health risks.

Derivation of the ATSDR MRL for Selenium

The Agency for Toxic Substances and Disease Registry (ATSDR) independently develops chemical-specific toxicity criteria based on non-cancer health effects. The ATSDR values are termed Minimal Risk Levels (MRLs), and are defined as "an estimate of daily human exposure to a substance that is likely without an appreciable risk of adverse effects (non-carcinogenic) over a specified duration of exposure." For selenium, ATSDR developed an MRL of 0.005 mg/kg-day for chronic oral exposures. Similar to US EPA's approach, ATSDR's chronic MRL for selenium is based on a NOAEL of 819 μg/day (0.015 mg/kg-day), which is the dose where symptoms of selenosis are no longer observed in the Chinese population highly exposed to selenium (Yang and Zhou, 1994). This NOAEL was divided by a UF of 3 (to account for human variability) to arrive at a chronic MRL value of 0.005 mg/kg-day.

Evaluation of Cancer Risks

There is no evidence to suggest that selenium is a human carcinogen (see above; ATSDR, 2003; IARC, 1975). As described earlier, epidemiological evidence suggests that selenium may actually contribute to a reduction in carcinomas of the lung, colorectal region, and prostate

(Clark *et al*., 1996; Combs *et al.*, 1997). In animals, selenium sulfide and ethyl selenac (selenium diethyldithiocarbamate) administered orally have been shown to be carcinogenic in rodents (Innes *et al*., 1969; NCI, 1968, as reported by ATSDR, 2003). Human exposure to these species of selenium compounds is extremely unlikely (ATSDR, 2003). Animal studies that have evaluated sodium selenate, sodium selenite, or organic forms of selenium have generally reported negative results for the development of cancer (ATSDR, 2003).

Based on the available human and animal evidence, various agencies make determinations regarding the carcinogenic potential of compounds. Based on the evidence available for selenium (inorganic and organic), US EPA has determined that selenium compounds (with the exception of selenium sulfide) are in Class D – not classifiable as to human carcinogenicity (US EPA, 2002a). In essence, this means that there are either too few data to reach a conclusion, or the data are conflicting. As a consequence of this classification, US EPA has not developed a CSF for selenium and does not require that selenium carcinogenicity be evaluated in standard risk assessments. The evidence for carcinogenicity of selenium sulfide, however, is sufficient to classify it as Group B2 (probable human carcinogen) (US EPA, 2002a).

The International Agency for Research on Cancer (IARC) has also concluded that selenium is "Not Classifiable to its Carcinogenicity to humans." In making this determination, IARC stated that, "The available data provide no suggestion that selenium is carcinogenic in man, and the evidence for a negative correlation between regional cancer death rates and selenium is not convincing" (IARC, 1975).

Regulations and Screening Criteria for Selenium in Tap Water and Soils

Regulatory standards and criteria for environmental media are derived using toxicity criteria (RfDs and CSFs), human exposure assumptions, and other information. For drinking water, US EPA establishes Maximum Contaminant Level Goals (MCLGs) and Maximum Contaminant Levels (MCLs). An MCLG is a non-enforceable regulatory standard that, according to US EPA, reflects "the maximum level of a contaminant in drinking water at which no known or anticipated adverse effect on the health of persons would occur, and which allows an adequate margin of safety" (US EPA, 2009a; US EPA, 2009b; US EPA, 2009c). Establishing a non-enforceable (and non-achievable) MCLG is consistent with US EPA's general regulatory approach for drinking water contaminants. For most water contaminants, US EPA also establishes an enforceable standard called an MCL. An MCL is set as close to the MCLG as possible while considering factors such as feasibility and cost-benefit. US EPA has established an MCLG of 0.05 mg/L (50 μg/L) and an MCL[3] of 0.05 mg/L (50 μg/L) for selenium (US EPA, 2009a). The MCL and the MCLG are the same because US EPA believes that, given present technology and resources, this is the lowest level to which water systems can reasonably be required to remove selenium should it occur in drinking water (US EPA, 2009a). These values were derived in a 1991 criteria document where US EPA assumed selenium toxicity became observable at 3.2 mg/day in a 70 kg adult. An uncertainty factor of 15 was applied to this value. The resulting value of 0.05 mg/L reflected the further assumptions that an individual drank 2

L/day and that only 50% of selenium would come from water consumption (*i.e.*, the relative source contribution was 50%) (US EPA, 2009d).

US EPA has also developed national recommended water quality criteria for the protection of aquatic life and human health in surface water. These Ambient Water Quality Criteria (AWQC) serve as non-enforceable recommendations and are developed by US EPA based on human health risk assessments, without consideration of technological feasibility or economic impact (US EPA, 2000). US EPA has developed an AWQC[3] of 170 µg/L for selenium to protect human health (US EPA, 2009c). US EPA assumes that surface water is potable, and that organisms living in water systems will be consumed in the diet. This value is based on RfD (0.005 mg/kg-d) – it assumes a 70-kg person drinks 2 L/day and no contribution of selenium from other sources. It also considers water use for agriculture and recreational purposes. Additionally, the AWQC establishes selenium levels to protect plants and animals in the environment. These criteria are discussed in more depth in Section 3.

Regional US EPA agencies have also developed screening levels for environmental media (*e.g.,* air, water, soil). At one time, each region developed and relied on a different set of screening criteria, but these analyses have recently been harmonized into a common set of screening criteria called "Regional Screening Levels" (RSLs). The tapwater RSL[3] for selenium is 180 µg/L, similar to the AWQC value (US EPA Region IX, 2009).

Soil Screening Levels (SSLs) are non-enforceable risk-based values for permissible levels of chemicals in soil developed by US EPA's Office of Solid Waste and Emergency Response (OSWER). They are used to screen sites to determine whether chemical concentrations in soil are high enough to warrant a further risk evaluation. SSLs are based on reasonable maximum exposure (RME) scenarios for residential settings, and are derived to reflect exposure concentrations that will not exceed a hazard quotient of 1 for non-carcinogens or a cancer risk of $1x10^{-6}$ for carcinogens (US EPA, 1996). SSLs have been developed by US EPA using default exposure values and are acknowledged to be conservative and, thus, health-protective for the majority of sites (US EPA, 1996). As noted by US EPA (1996), an exceedance of an SSL does not automatically trigger remediation activities, but rather indicates that further evaluation of the site is warranted to determine if remediation is necessary. In 2002, OSWER published supplemental guidance for developing SSLs as a companion to the 1996 guidance (US EPA, 2002b). This guidance builds upon the soil screening framework for residential land use scenarios established in the original guidance, adding new scenarios for soil screening evaluations. It also updates the residential scenario in the 1996 guidance, adding exposure pathways and incorporating new modeling data. The SSLs for selenium, as established by US EPA, are 390 mg/kg for residential areas and 5,700 mg/kg for industrial and commercial areas (US EPA, 2002b).

[3] The methodologies used to estimate the MCL, AWQC, and RSL incorporate varying exposure assumptions for drinking water intake rates and relative source contribution factors (*i.e.*, the amount consumed from a particular source), therefore the estimated values will be different and are dependent on the assumptions used in each calculation.

Regional US EPA agencies have also developed screening levels for soil (residential and industrial). The soil RSLs for selenium in US EPA Region IX are 390 mg/kg (residential) and 5,100 mg/kg (industrial) (US EPA Region IX, 2009). Some states may also develop their own screening criteria that may differ from US EPA values. For example, California has developed California Human Health Screening Levels (CHHSLs). The CHSSLs for selenium are 380 mg/kg (residential) and 4,800 mg/kg (industrial/commercial), which differ slightly from US EPA's screening values (CalEPA, 2005).

In addition to the direct contact scenarios, the agencies also develop soil screening criteria to protect groundwater from chemicals that may leach. OSWER has developed SSLs for two dilution attenuation factors (DAFs): 1 and 20 (US EPA, 2002b). A DAF of 1 means that essentially all of the chemical present in soil (1/1) will leach into the groundwater underneath the contaminated soils (*i.e.*, no dilution or attenuation occurs between the source and the groundwater well). A DAF of 20 assumes that only $1/20^{th}$ of the chemical present in soils will reach a groundwater well (*i.e.*, the contaminant concentration is reduced before reaching the groundwater due to natural processes occurring in the subsurface). Although the DAF varies widely from chemical to chemical and is dependent on numerous variables such as soil characteristics and depth to groundwater, US EPA has assumed that all chemicals have a DAF of 1 or 20. US EPA has determined residential soil screening values for selenium of 5 mg/kg using a DAF of 20, and of 0.3 mg/kg using a DAF of 1 (US EPA, 2002b). The SSL using a DAF of 1 (0.3 mg/kg) is within average background concentrations of selenium in the US (see Section 1).

Regional US EPA offices have taken a slightly different approach regarding soil screening criteria that are protective of groundwater. The RSLs include soil screening values to account for leaching to groundwater to meet the MCL as well as a risk-based concentration (based on meeting an acceptable cancer or non-cancer risk target). The RSL values assume that no dilution attenuation occurs. The soil RSL values for selenium are 0.95 mg/kg (risk-based) and 0.26 mg/kg (MCL-based) (US EPA Region IX, 2009). Documentation for the RSL table points out that these screening levels "were designed for use during the early stages of a site evaluation when information about subsurface conditions may be limited. Because of this constraint, the equations used are based on conservative, simplifying assumptions about the release and transport of contaminants in the subsurface" (US EPA Region III, 2009).

Table 2-4 summarized representative US soil screening levels for selenium.

Table 2-4
Summary of Soil Screening Criteria

	Residential	Industrial
Protection from Direct Contact with Selenium in Soil		
US EPA Soil Screening Level (mg/kg)	390	5,700
US EPA Regional Screening Levels (mg/kg)	390	5,100
California Human Health Screening Levels (mg/kg)	380	4,800
Protection for Leaching to Groundwater		
US EPA Soil Screening Level (mg/kg)	5	Residential and Industrial/Commercial (DAF = 20)
	0.3	Residential and Industrial/Commercial (DAF=1)
Regional Screening Levels (mg/kg)	0.95	Risk-based (DAF=1)

Human Health Risk Assessment Toolbox

Government websites and reports provide useful information on risk assessment. The list below presents some of the key human health risk assessment resources. Some resources are specific to selenium, while others present information on a wide range of environmental contaminants.

Selenium-specific Resources

US EPA's IRIS file for Selenium and Compounds (CASRN - 7782-49-2) (US EPA, 2002a)
Website: http://www.epa.gov/ncea/iris/subst/0472.htm

Agency for Toxic Substances and Disease Registry's Toxicological Profile for Selenium (ATSDR, 2003)
Website: http://www.atsdr.cdc.gov/toxprofiles/tp92-p.pdf

US EPA's Ground Water and Drinking Water Consumer Fact Sheet on Selenium (US EPA, 2006)
Website: http://www.epa.gov/ogwdw/pdfs/factsheets/ioc/selenium.pdf

National Institutes of Health's "Dietary Supplement Fact Sheet, Selenium" (NIH, 2009)
Website: http://dietary-supplements.info.nih.gov/factsheets/selenium.asp

Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (IOM, 2000)
Website: http://www.nal.usda.gov/fnic/DRI//DRI_Vitamin_C/vitamin_c_full_report.pdf

General Resources

US EPA's Soil Screening Guidance: Technical Background Document (US EPA, 1996)
Website: http://www.epa.gov/superfund/health/conmedia/soil/toc.htm

US EPA's Supplemental Guidance for Developing Soil Screening Levels for Superfund Sites (US EPA, 2002b)
Website: http://www.epa.gov/superfund/health/conmedia/soil/pdfs/ssg_main.pdf

Current National Recommended Water Quality Criteria (US EPA, 2009b)
Website: http://www.epa.gov/waterscience/criteria/wqctable/nrwqc-2009.pdf

US EPA Region IX Regional Screening Level (RSL) Table (US EPA Region IX, 2009)
Website: http://www.epa.gov/reg3hwmd/risk/human/rb-concentration_table/Generic_Tables/pdf/master_sl_table_run_DECEMBER2009.pdf

3
ECOLOGICAL EFFECTS AND RISK ASSESSMENT

Consistent with the human health information, selenium is an essential nutrient for animals, but it can be toxic in excess (Chapman *et al*., 2009). Selenium-induced toxicity in wildlife may occur via water, sediment, and soil exposure, but the principal route of selenium exposure in higher animals is through the diet. Selenium poses the greatest concern to aquatic environments (*i.e.*, surface waters), which can receive selenium from natural weathering processes, fossil fuel combustion, mining/refining/smelting activities, agricultural runoff, animal feed and human supplements production and usage, other selenium-enhanced personal care products, and nanomaterials (Chapman, 2009). Hence, selenium uptake, bioaccumulation, and toxicity in aquatic organisms are the primary focus of this section; however, an overview of selenium toxicity to terrestrial plants, invertebrates, birds, and mammals is also presented.

The following sections discuss selenium uptake and bioaccumulation, selenium ecotoxicity, and reported wildlife effects following exposure to anthropogenic selenium. This discussion is followed by an overview of ecological screening benchmarks (*i.e.*, threshold concentrations above which effects might occur) for selenium and regulatory guidelines for the protection of wildlife.

Selenium Uptake and Bioaccumulation

The importance of the dietary route of exposure for selenium necessitates an understanding of the trophic transfer of selenium from primary producers to top predators. Available bioconcentration and bioaccumulation data for aquatic species are presented in Table 3-1. Bioconcentration Factors (BCF) represent selenium uptake via water-only exposure, while Bioaccumulation Factors (BAF) represent selenium uptake via dietary and waterborne exposures. Because fish are typically secondary or tertiary consumers, dietary exposure is expected to be an important contributor of selenium bioaccumulation in fish in natural environments. In the laboratory, however, water-only exposures can be maintained to estimate a fish BCF. Comparing field and laboratory results (as shown in Table 3-1) demonstrates that fish BAFs are indeed much higher than BCFs—indicating the importance of dietary exposures in selenium uptake by fish.

Although the field studies in Table 3-1 indicate that BAFs for insects are generally higher than those for fish, there is significant variability within fish and insects: Field-based fish BAFs range from 273 to 6,538 L/kg and insect BAFs range from 969 to 31,800 L/kg. BCFs for algae and plants are higher than BCFs in fish (in both laboratory and field studies), indicating that selenium bioaccumulation occurs primarily at the base of the food chain. Besser *et al*. (1993 as cited by

US EPA, 2004) simulated a water → algae → zooplankton (daphnid) → fish (bluegill) food chain for selenium uptake and bioaccumulation. At 10 µg Se/L, the algae BCFs were 1,440 and 428 L/kg for selenite and selenate, respectively. However, the algae to daphnid and daphnid to bluegill concentration factors were 0.61 and 0.51, respectively—indicating that biomagnification[4] did not occur in these trophic transfers. The overall bluegill BAF for selenium was 550 L/kg when the entire algae-daphnia-bluegill food chain was exposed to 10 µg/L of 1:1 selenite and selenate concentration.

[4] Biomagnification is the progressive increase in concentration of a substance that occurs in a food chain (*i.e.*, higher-trophic-level receptors in the food chain have higher concentrations than lower-trophic-level receptors).

Table 3-1
Bioconcentration and Bioaccumulation of Selenium by Aquatic Organisms

Organisms	Selenium Species	Water Concentration (µg Se/L)	Duration (Days)	Tissue Concentration[1] (µg Se/g dw)	BCF[2] (L/kg)	BAF[3] (L/kg)	Reference (Citations provided in US EPA, 2004)
Laboratory Derived							
Fish							
Rainbow trout (*Oncorhynchus mykiss*)	Sodium selenite		48		10 (2)		Adams (1976)
		100	28	2.3	23		Gissel-Nielsen and Gissel-Nielsen (1978)
			308		42		Hodson *et al.* (1980)
		21	90	0.64	30.5		Hunn *et al.* (1987)
Fathead minnow (*Pimephales promelas*)	Sodium selenite		96		17.6 (11.6)		Adams (1976)
	Sodium selenate	10.7	56		52		Bertram and Brooks (1986)
		21.5	56		26		Bertram and Brooks (1986)
		43.5	56		21		Bertram and Brooks (1986)

Table 3-1 (continued)
Bioconcentration and Bioaccumulation of Selenium by Aquatic Organisms

Organisms	Selenium Species	Water Concentration (µg Se/L)	Duration (Days)	Tissue Concentration[1] (µg Se/g dw)	BCF[2] (L/kg)	BAF[3] (L/kg)	Reference (Citations provided in US EPA, 2004)
Bluegill (*Lepomis macrochirus*)	Selenious acid		28		20		Barrows *et al.* (1980)
	Sodium selenite	10	120		430-470		Lemly (1982)
	Selenate	10	30		56		Besser *et al.* (1993)
	Selenite	10	30		56		Besser *et al.* (1993)
	Selenite: selenate 1:1	10	30			550	Besser *et al.* (1993)
Largemouth bass (*Micropterus salmoides*)	Sodium selenite	10	120		270-310		Lemly (1982)
Razorback sucker (*Xyrauchen texanus*)	Selenate: selenite 6:1	76	90	3.2	42		Hamilton *et al.* (2000)
Bonytail (*Gila elegans*)	Selenate: selenite 6:1	73	90	2.2	30		Hamilton *et al.* (2000)
Plant							
Algae (*Chlamydononas reinhardtii*)	Selenite	10	4		1,440		Besser *et al.* (1993)
	Selenate	10	4		428		Besser *et al.* (1993)

Table 3-1 (continued)
Bioconcentration and Bioaccumulation of Selenium by Aquatic Organisms

Organisms	Selenium Species	Water Concentration (µg Se/L)	Duration (Days)	Tissue Concentration[1] (µg Se/g dw)	BCF[2] (L/kg)	BAF[3] (L/kg)	Reference (Citations provided in US EPA, 2004)
Crustacean							
Cladoceran (*Daphnia magna*)	Selenite: selenate 1:1	156	21	14.7	94		Ingersoll *et al.* (1990)
		348	21	31.7	91		Ingersoll *et al.* (1990)
	Selenate/ selenite	10	4		293-570		Besser *et al.* (1993)
Bivalve							
Clam (*Corbicula fluminae*)	Selenomethionine	50	20			770	Adam-Guillernin *et al.* (2009)
Field Derived							
Fish							
Bluegill (*Lepomis macrochirus*)	Selenite	2.5	221	4.825		1,930	Hermanutz *et al.* (1996)
Various fish species[4]	Natural (not speciated)	11	Field	3-5.1		273-464	Garcia-Hernandez *et al.* (2000)
Cutthroat trout (*Oncorhychus clarki*)	Natural (not speciated)	13.9	Field	(-12.5)		(899)	Kennedy *et al.* (2000)
Various fish species[5]	Natural (not speciated) Herrington Creek, MD	0.33	Field	1.35-1.94		4,091-5879	Mason *et al.* (2000)

Table 3-1 (continued)
Bioconcentration and Bioaccumulation of Selenium by Aquatic Organisms

Organisms	Selenium Species	Water Concentration (µg Se/L)	Duration (Days)	Tissue Concentration[1] (µg Se/g dw)	BCF[2] (L/kg)	BAF[3] (L/kg)	Reference (Citations provided in US EPA, 2004)
Various fish species[6]	Natural (not speciated) Blacklick Run, MD	0.39	Field	1.79-2.55		4,590-6,538	Mason *et al.* (2000)
Insect							
Ephemeroptera (Mayflies, Insects)	Selenite	2.5	221	5.05		1,957	Hermanutz *et al.* (1996)
	Natural (not speciated) Herrington Creek, MD	0.33	Field	5.05		17,600	Mason *et al.* (2000)
Heptageniidae (Mayflies, Insects)	Selenite	10	221	17.3		1,787	Hermanutz *et al.* (1996)
	Natural (not speciated) Blacklick Run, MD	0.39	Field	5.8		14,900	Mason *et al.* (2000)
Chironomidae (non-biting midges, Insects)	Natural (not speciated)	1.58	3 yr	10.4		6,582	Zhang and Moore (1996)
		14.5	3 yr	24.7		1,703	Zhang and Moore (1996)
	Selenite	2.5	221	3.61		1,399	Hermanutz *et al.* (1996)
		10	221	13.6		1,405	Hermanutz *et al.* (1996)

Table 3-1 (continued)
Bioconcentration and Bioaccumulation of Selenium by Aquatic Organisms

Organisms	Selenium Species	Water Concentration (µg Se/L)	Duration (Days)	Tissue Concentration[1] (µg Se/g dw)	BCF[2] (L/kg)	BAF[3] (L/kg)	Reference (Citations provided in US EPA, 2004)
Hydropsychidae (caddisflies, Insects)	Natural (selenite: selenate 9:1)	32	NA	3.1		969	Reash *et al.* (1999)
	Natural (not speciated) Herrington Creek, MD	0.33	Field	10.5		31,800	Mason *et al.* (2000)
	Natural (not speciated) Blacklick Run, MD	0.39	Field	4.6		11,800	Mason *et al.* (2000)
Crustacean							
Astacidae (crayfish, Crustaceans)	Natural (not speciated) Herrington Creek, MD	0.33	Field	1.275		3,864	Mason *et al.* (2000)
	Natural (not speciated) Blacklick Run, MD	0.39	Field	0.405		1,038	Mason *et al.* (2000)

Table 3-1 (continued)
Bioconcentration and Bioaccumulation of Selenium by Aquatic Organisms

Organisms	Selenium Species	Water Concentration (µg Se/L)	Duration (Days)	Tissue Concentration[1] (µg Se/g dw)	BCF[2] (L/kg)	BAF[3] (L/kg)	Reference (Citations provided in US EPA, 2004)
Plant and other							
Periphyton (algae, bacteria, *etc.*)	Natural (not speciated) Herrington Creek, MD	0.33	Field	2.86	8,667		Mason *et al.* (2000)
	Natural (not speciated) Blacklick Run, MD	0.39	Field	0.245	628		Mason *et al.* (2000)
Bryophytes (non-vascular plants)	Natural (not speciated) Herrington Creek, MD	0.33	Field	1.86	5,636		Mason *et al.* (2000)
	Natural (not speciated) Blacklick Run, MD	0.39	Field	0.78	2,000		Mason *et al.* (2000)

Notes:

[1] Whole-body tissue concentrations; tissue concentrations based on muscle are shown in parentheses

[2] BCF: Bioconcentration factor = concentration in tissue/concentration in water (no selenium-contaminated diet involved); BCFs based on muscle tissue are shown in parentheses

[3] BAF: Bioaccumulation factor = concentration in tissue/concentration in water (dietary uptake is involved); BAFs based on muscle tissue are shown in parentheses

[4] Tilapia species, Carp (Caprinus carpio), Largemouth bass (Micropterus salmoides)

[5] Brown bullhead (Ictalurus nebulosus), White sucker (Catostomus commersoni), Brook trout (Salvelinus fontinalis), Creek chub (Semotilus arromaculatus)

[6] Mottled sculpin (Cottus bairdi), Blacknose dace (Rhinchthus atratulus), Brook trout (Salvelinus fontinalis)

Source: US EPA (2004)

The single largest step in selenium bioaccumulation occurs at the base of food webs, *i.e.*, in primary producers (bacteria, fungi, algae, and plants). In aquatic environments, the primary producers assimilate inorganic selenium rapidly and efficiently and transform inorganic selenium into organic selenium species—which are then transferred throughout the food web via diet to primary and secondary consumers (invertebrates and vertebrates) (Chapman *et al*., 2009). Because dietary exposure generally dominates the selenium bioaccumulation process, using selenium water concentrations to predict selenium toxicity is not reliable. Additionally, there is evidence that the extent of selenium bioaccumulation depends on selenium speciation, exposure concentration, and exposure duration. The magnitude of these influences, however, is not well understood. As discussed further below, the importance of the dietary exposure route has resulted in the development of chronic benchmarks related to tissue residues rather than dissolved selenium concentrations in water for organisms in aquatic environments.

Environmental Factors Affecting Selenium Uptake, Bioaccumulation, and Toxicity

As mentioned above, field observations show no clear relationship between water concentration, selenium uptake, and hence selenium chronic toxicity (Chapman *et al*., 2009), indicating that other environmental factors influence selenium uptake and toxicity. Some of these factors, such as selenium speciation (selenate *vs*. selenite) and sulfate concentrations, are discussed below. Water hardness and other metal concentrations may also influence selenium uptake and toxicity.

It is well known that water hardness (*i.e*., water with high mineral content) influences the aquatic toxicity of trace metals such as copper, cadmium, nickel, and zinc. Accordingly, it appears that water hardness also plays a role in the aquatic toxicity of selenium. The effects of water hardness, however, appear to depend on selenium speciation and species of organism, but with no consistent beneficial or adverse impact. For example, water hardness did not affect the toxicity of Se (II) and Se (VI) to *D. magna*, but Se (IV) and a 1:1 mixture of Se (IV) and Se (VI) were about twice as toxic in hard water (134 mg/L $CaCO_3$) than in soft water (46 mg/L $CaCO_3$) (Ingersoll *et al*., 1990, as cited by US EPA, 2004). In contrast to *D. magna*, Se (IV) was twice as toxic toward young striped bass (*M. saxatilis*) in soft water (40 mg/L $CaCO_3$) than in hard water (285 mg/L $CaCO_3$) (Palawaski *et al*., 1985, as cited by US EPA, 2004). In a study of Chinook salmon and Coho salmon, the toxicity of a 1:1 mixture of selenate and selenite did not differ in soft and hard water (Hamilton and Buhl, 1990, as cited by US EPA, 2004).

Selenium exposure generally occurs in conjunction with other metals; therefore, the influence of metals on selenium ecotoxicity is relevant to understanding environmental risks. Selenium has been observed to act antagonistically with mercury (Hg), cadmium (Cd), and arsenic (As) (Ohlendorf, 2002; US EPA, 2004). Because both Hg and Cd are also potentially toxic, selenium may have a protective effect. For example, it has been suggested that the protective effect of selenite on Hg^{2+} toxicity in mammals is due mainly to the *in vivo* formation of mercuric selenide (HgSe)—a stable and biologically inert complex (Yang *et al*., 2008). Several studies have reported that increased selenium in food and/or water lowered Hg uptake by aquatic organisms including fish (Turner and Swick, 1983, Paulsson and Lundberg, 1989, Southworth *et al*., 2000,

Chen *et al*., 2001, all as cited by Yang *et al*., 2008; Sackett *et al*., 2010), oligochaetes (Nuutinen and Kukkonen, 1998, as cited by Yang *et al*., 2008), and amphipods (Belzile *et al*., 2006, as cited by Yang *et al*., 2008).

Selenium Ecotoxicity

This section presents data sources that were used to compile selenium ecotoxicity information, and summarizes acute and chronic selenium toxicity data for a wide range of aquatic and terrestrial organisms.

Data Sources

Ecotoxicity data are generally collected for species considered to be representative of each trophic level (*i.e.*, a species' position in the food chain) within an ecosystem. For aquatic ecosystems, phytoplankton and algae (*e.g.*, the green alga *Pseudokirchneriella subcapitata*) represent primary producers, whereas zooplankton (*e.g.*, the small crustacean *Daphnia magna*) and fish (*e.g.*, the fathead minnow *Pimephales promelas*) represent primary and secondary consumers, respectively. Consequently, ecotoxicity data obtained for algae, daphnids, and fish are considered sufficiently representative for evaluating the aquatic toxicity of a chemical.

AWQC for the protection of aquatic organisms are developed by US EPA to ensure protection of our nation's waters under the Clean Water Act (US EPA, 2009b). Documents in support of the AWQC provide a comprehensive evaluation of chemical-specific ecotoxicity data and were relied on as a source of aquatic toxicity information. The latest version of AWQC was published in 2004 and includes a comprehensive review of existing selenium aquatic ecotoxicity data up until the date of publication (US EPA, 2004). It is anticipated that a revision of the selenium criteria document will be released by US EPA in 2010.

Since the publication of the 2004 draft AWQC, the focus of selenium ecotoxicity studies has been on bioaccumulation and chronic criteria development. A search for post-2004 selenium aquatic ecotoxicity data (all acute and chronic endpoints) in the ECOTOX database (US EPA, 2007a) resulted in only two studies. Consequently, our evaluation of acute aquatic effects is focused on the information presented in the 2004 AWQC report, but it also includes key post-2004 studies included in the US EPA's portal for selenium AWQC (US EPA, 2008a).

For our review of selenium ecotoxicity to terrestrial species, we relied primarily on the most recent Ecological Soil Screening Level (Eco-SSL) document published by US EPA (US EPA, 2007b). Eco-SSLs are concentrations of contaminants in soil that are protective of ecological receptors that commonly come into contact with and/or consume biota that live in or on soil. Eco-SSLs are derived separately for four groups of ecological receptors: plants, soil invertebrates, birds, and mammals. As such, these values are presumed to provide adequate protection of terrestrial ecosystems. The detailed procedures for deriving Eco-SSLs are described in US EPA (2003) and include an extensive search of the technical literature for selenium terrestrial ecotoxicity data.

In light of the data sources used for obtaining aquatic and terrestrial selenium ecotoxicity information, it can be assumed that our review is extensive and even comprehensive, but by no means exhaustive.

Aquatic Toxicity of Selenium

Acute toxicity of selenium primarily occurs via water exposure, whereas chronic toxicity of selenium primarily occurs via dietary exposure. Acute toxicity of selenium to aquatic animals and plants is discussed below, followed by a review of chronic aquatic toxicity of selenium.

Acute Toxicity of Selenium to Aquatic Organisms

Tables 3-2 [selenite – Se(IV)] and 3-3 [selenate – Se(VI)] provide summaries of selenium toxicity data for aquatic animals considered acceptable by US EPA (2004) for the purpose of deriving acute AWQC. Selenium toxicity is presented separately for selenate and selenite since these are the two primary oxidation states of selenium encountered in the aquatic environment. Selenate is expected to be the predominant oxidation state at chemical equilibrium in oxic alkaline waters. However, the slow conversion rate of selenite to selenate in natural waters may result in a significant presence of selenite. The acute toxicity values presented in Tables 3-2 and 3-3 are based on what was initially introduced in the laboratory tests and assume insignificant chemical transformation during the test (US EPA, 2004).

Table 3-2
Acute Aquatic Toxicity of Selenite [Se(IV)]

Species/General	LC50 or EC50[1] (µg Se/L)	SMAV[2] (µg Se/L)	GMAV[3] (µg Se/L)
Freshwater Organisms			
Invertebrates			
Hyalella sp. (amphipod)	340-670	461	461
Ceriodaphnia sp. (cladoceran)	440-720	440-<604	< 515
Daphnia sp. (cladoceran)	215-3,870	905-1987	905
Hydra sp. (hydra)	1,700	1,700	1,700
Gammarus sp. (amphipod)	1,800-10,950	3,489	3,489
Tubifex sp. (worm)	7,710	7,710	7,710
Physa sp. (snail)	24,100	24,100	24,100
Aplexa sp. (snail)	23,000-53,000	34,914	34,914
Nephelopsis sp. (leech)	203,000	203,000	203,000

Table 3-2 (continued)
Acute Aquatic Toxicity of Selenite [Se(IV)]

Species/General	LC50 or EC50[1] (µg Se/L)	SMAV[2] (µg Se/L)	GMAV[3] (µg Se/L)
Fish			
Morone sp. (striped bass)	1,325-2,400	1,783	1,783
Pimephales sp. (fathead minnow)	620-5,200	2,209	2,209
Jordanella sp. (flagfish)	6,500	6,500	6,500
Xyrauchen sp. (razorback sucker)	4,067-11,300	7,679	7,679
Gilas sp. (bonytail)	6,855-14,490	9,708	9,708
Salvelinus sp. (brook trout)	10,200	10,200	10,200
Oncorhynchus sp. (salmonid)[4]	1,800->348,320	7,240-15,596	10,580
Notemigonus sp. (golden shiner)	11,200	11,200	11,200
Perca sp. (yellow perch)	11,700	11,700	11,700
Gambusia sp. (mosquito fish)	12,600	12,600	12,600
Ptychocheilus sp. (squawfish)	6,398-20,700	12,801	12,801
Ictalurus sp. (catfish)	4,110-13,600	13,600	13,600
Thymallus sp. (greyling)	15,675-34,732	15,675	15,675
Catostomus sp. (sucker)	19,100-31,400	19,100-30,176	24,008
Carassius sp. (goldfish)	26,100	26,100	26,100
Lepomis sp. (bluegill)[5]	12,000-28,500	28,500	28,500
Caprinus sp. (carp)	35,000	35,000	35,000
Chironomus sp. (midge)	24,150-48,200	25,934-48,200	35,356
Tanytarsus sp. (midge)	42,500	42,500	42,500
Final Acute Value (FAV)			**514.9**
Saltwater Organisms[6]			
Invertebrates			
Argopecten sp. (bay scallop)	255	255	255
Cancer sp. (dungeness crab)	1,040	1,040	1,040
Penaeus sp. (brown shrimp)	1,200	1,200	1,200
Acartia sp. (copepod)	839-2,110	839-2,110	1,331

Table 3-2 (continued)
Acute Aquatic Toxicity of Selenite [Se(IV)]

Species/General	LC50 or EC50[1] (µg Se/L)	SMAV[2] (µg Se/L)	GMAV[3] (µg Se/L)
Americamysis sp. (mysid)	600-1,500	1,500	1,500
Spisula sp. (surf clam)	1,900	1,900	1,900
Callinectes sp. (blue crab)[4]	4,600	4,600	4,600
Crassostrea sp. (Pacific oyster)[4]	>10,000	>10,000	>10,000
Mytilus sp. (blue mussel)[4]	>10,000	>10,000	>10,000
Fish			
Melanogrammus sp. (haddock)	599	599	599
Morone sp. (striped bass)	1,550-3,900	3,036	3,036
Paralichthys sp. (summer flounder)[4]	3,497	3,497	3,497
Cyprinodon sp. (sheepshead minnow)	6,700-7,400	7,400	7,400
Menidia sp. (Atlantic silverside)	9,725	9,725	9,725
Pseudopleuronectes sp. (winter flounder)[4]	14,240-15,070	14,649	14,649
Apeltes sp. (stickleback)	17,350	17,350	17,350
Final Acute Value (FAV)			**253.4**

Notes:

[1] LC50: 50% lethality concentration; EC50: 50% effective concentration (both LC50 and EC50 are adjusted to sulfate = 100 mg/L)

[2] Species mean acute values (adjusted to sulfate = 100 mg/L)

[3] Genus mean acute values (adjusted to sulfate = 100 mg/L)

[4] Commercially important species

[5] Recreationally important species

[6] Salinity ranged from 1-34 g/kg.

Source: US EPA (2004)

In Tables 3-2 and 3-3, the toxicity values are adjusted to a sulfate (SO_4^{2-}) concentration of 100 mg/L sulfate. This is because higher sulfate concentrations are observed to mitigate the acute toxicity of selenium, particularly that of selenate. The ionic radius of selenate (SeO_4^{2-}) that predominates in well-aerated surface waters is comparable to that of sulfate (Frausto da Silva and Williams, 1991, as cited by US EPA, 2004), and cellular uptake is expected to take place via the same ion transport channels or permeases for both oxyanions. Competitive uptake of sulfate and

selenate has been observed in a number of species including algae, aquatic plants, crustaceans, fungi, and wheat (Riedel and Sanders, 1996, Bailey *et al*., 1995, Olge and Knight, 1996, Riedel and Sanders, 1996, Bailey *et al*., 1995, Olge and Knight, 1996, Gharieb *et al*., 1995, Richter and Bergmann, 1993, Hansen *et al*., 1993, all as cited by US EPA, 2004). A significant relationship has been demonstrated between acute selenate toxicity to aquatic organisms and ambient sulfate concentrations (Brix *et al*., 2001 as cited by US EPA, 2004). Consequently, US EPA (2004) standardized selenium acute toxicity values at 100 mg/L sulfate.

Acute toxicity of selenite to freshwater invertebrates ranges from 215 µg/L for a cladoceran (*Daphnia magna*) to 203,000 µg/L for a leech (*Nephelopsis obscura*). A wide range of sensitivity is also observed in freshwater fish, with acute toxicity ranging from 620 µg/L for fathead minnow (*Pimephales promelas*) to > 348,320 µg/L for Chinook salmon (*Oncorhynchus tshawytscha*). As shown in Table 3-2, freshwater invertebrates represent the four most sensitive genera (*i.e.*, lowest GMAV values).[5]

Saltwater species also vary widely in their sensitivity toward selenite (Table 1-2). Acute toxicity values for invertebrates range from 255 µg Se/L for juvenile bay scallop (*Argopecten irradians*) to > 10,000 µg Se/L for blue mussel (*Mytilus edulis*). In saltwater fish, toxicity is observed from 599 µg Se/L for haddock larvae (*Melanogrammus aeglefinus*) to 17,350 µg Se/L for four-spined sticklebacks (*Apeltes quadracus*).

Data on selenate toxicity on saltwater species are available for only one species (Table 3-3). Acute toxicity of selenate to freshwater invertebrates ranges from 593 µg Se/L for a cladoceran (*Daphnia pulicaria*) to 1,515,616 µg Se/L for a leech (*Nephelopsis obscura*). Acute toxicity of selenate to freshwater fish ranges from 10,305 µg Se/L for the razorback sucker (*Xyrauchen texanus*) to 226,320 µg Se/L for channel catfish (*Ictalurus punctatus*).

Saltwater species appear to be more sensitive than freshwater species to selenium, *i.e.*, the selenate final acute value (FAV) for saltwater species is lower than the selenate FAV for freshwater species. Species mean acute values (SMAV) for both selenite and selanate have been determined for 20 freshwater species within 18 genera and for one saltwater species. Of these 21 species, 20 are more sensitive toward the effects of selenite. Only the amphipod *G. pseudolimnaeus* is more sensitive to selenate than selenite. The FAV for selenite and selenate are consistent with these observations, *i.e.*, the freshwater selenite FAV (514.9 µg Se/L) is lower than the freshwater selenate FAV (834.4 µg Se/L).

[5] Species mean acute values (SMAVs) and genus mean acute values (GMAVs) are determined in accordance with the guidelines (Stephan *et al*., 1985) to derive numerical AWQC for the protection of aquatic wildlife. Toxicity values for the eight most sensitive genera as well as endangered and commercially important genera are used to derive a final acute value (FAV) which is then divided by two to arrive at the acute AWQC.

Table 3-3
Acute Aquatic Toxicity of Selenate [Se(VI)]

General	LC50 or EC50[1] (µg Se/L)	SMAV[2] (µg Se/L)	GMAV[3] (µg Se/L)
Freshwater Organisms			
Invertebrates			
Ceriodaphnia sp. (cladoceran)	842-2,877	842	842
Hyalella sp. (amphipod)	723-4,224	1,397	1,397
Daphnia sp. (cladoceran)	593-14,482	593-3,420	1,887
Gammarus sp. (amphipod)	196-4,904	2,315-2,747	2,522
Hydra sp. (hydra)	25,031	25,031	25,031
Aplexa sp. (snail)	661,816	661,816	661,816
Nephelopsis sp. (leech)	1,515,661	1,515,661	1,515,661
Fish			
Xyrauchen sp. (razorback sucker)	5,523-16,184	10,309	10,309
Gila sp. (bonytail)	10,560-77,134	10,560	10,560
Pimephales sp. (fathead minnow)	7,286-18,860	11,346	11,346
Ptychocheilus sp. (Colorado squawfish)	9,842-103,786	18,484	18,484
Catostomus sp. (sucker)	27,380	27,380	27,380
Oncorhynchus sp. (salmonid)[4]	22,668->856,083	29,141-83,353	47,164
Chironomus sp. (midge)	50,727	50,727	50,727
Paratanytarsus sp. (midge)	68,582	68,582	68,582
Thymallus sp. (greyling)	70,182-126,328	94,159	94,159
Lepomis sp. (bluegill)[5]	216,033	216,033	216,033
Ictalurus sp. (catfish)[4]	226,320	226,320	226,320
Final Acute Value (FAV)			**834.4**
Saltwater Organism[6]			
Morone sp. (striped bass)	9,790-85,840	9,790	9,790

Table 3-3 (continued)
Acute Aquatic Toxicity of Selenate [Se(VI)]

Notes:

[1] LC50: 50% lethality concentration; EC50: 50% effective concentration (both LC50 and EC50 are adjusted to sulfate = 100 mg/L)

[2] Species mean acute values (adjusted to sulfate = 100 mg/L)

[3] Genus mean acute values (adjusted to sulfate = 100 mg/L)

[4] Commercially important species

[5] Recreationally important species

[6] Salinity ranged from 3.5-6.5 g/kg and LC50 and GMAV not adjusted for sulfate

Source: US EPA (2004)

Acute and Chronic Toxicity of Selenium to Aquatic Plants

Tables 3-4 and 3-5 provide summaries of toxicity data for aquatic plants as compiled by US EPA (2004). The lowest toxicity values reported are a selenate EC50 of 199 μg Se/L and a selenite No Observed Effect Concentration (NOEC) of 800 μg Se/L for green alga (*Selenastrum capricornutum*) and duckweed (*Lemna minor*), respectively (Richter, 1982, Jenner and Janssen-Mommen, 1993, both as cited by US EPA, 2004). Saltwater plants appear to be particularly insensitive toward selenium (both selenite and selenate), with reported NOECs ranging from about 1,000 μg Se/L to about 100,000 μg Se/L (Tables 3-4 and 3-5).

To summarize, selenium toxicity in aquatic plants and acute selenium toxicity in fish (typically in the mg/L range) is generally observed at concentrations significantly higher than those causing toxicity in some of the more sensitive aquatic invertebrates (typically in the μg/L range).

Table 3-4
Acute and Chronic Toxicity of Selenite [Se(IV)] to Aquatic Plants

Plant Species	Endpoints[1]	Concentration (µg Se/L)	Reference (Citations provided in US EPA, 2004)
Freshwater Species			
Green alga (*Chlorella ellipsoidea*)	EC50	70,000	Shabana and El Attar (1995)
Green alga (*Selenastrum capricornutum*)	EC50	2,900-65,000	Richter (1982); Ibrahim and Spacie (1990)
Blue-green alga (*Anabaena contricta*)	EC50	67,000	Shabana and El Attar (1995)
Blue-green alga (*Anabaena variabilis*)	LC50	15,000	Kumar and Prakash (1971)
Blue-green alga (*Anacystis nidulans*)	LC50	30,000	Kumar and Prakash (1971)
Duckweed (*Lemna minor*)	EC50	2,400-3,500	Wang (1986); Jenner and Janssen-Mommen (1993)
Duckweed (*Lemna minor*)	NOEC	800	Jenner and Janssen-Mommen (1993)
Saltwater Species			
Green alga (*Dunaliella teriolecta*)	NOEC	1,076	Wong and Oliveira (1991)
Cyanophyceae alga (*Agemenellum quadruplicatum*)	NOEC	10,761	Wong and Oliveira (1991)
Diatom (*Chaetoceros vixvisibilis*)	NOEC	1,076	Wong and Oliveira (1991)
Diatom (*Skeletonema costatum*)	EC50	7,930	US EPA (1978)
Dinoflagellate (*Amphidinium carterae*)	NOEC	10,761	Wong and Oliveira (1991)
Eustigmatophyceae alga (*Nannochloropsis oculata*)	NOEC	107,606	Wong and Oliveira (1991)
Prymnesiophyceae alga (*Isochrysis galbana*)	NOEC	1,076	Wong and Oliveira (1991)
Prymnesiophyceae alga (*Pavlova lutheri*)	NOEC	1,076	Wong and Oliveira (1991)

Notes: [1] EC50: 50% effective concentration; LC50: 50% lethal concentration; NOEC: No Observed Effect Concentration *Source: US EPA (2004)*

Table 3-5
Acute and Chronic Toxicity of Selenate [Se(VI)] to Aquatic Plants

Plant Species	Endpoint[1]	Concentration (µg Se/L)	Reference (Citations provided in US EPA, 2004)
Freshwater Species			
Green alga (*Selenastrum capricornutum*)	EC50	199-<40,000	Richter (1982); Ibrahim and Spacie (1990)
Blue-green alga (*Anacystis nidulans*)	EC50	39,000	Kumar and Prakash (1971)
Blue-green alga (*Anabaena viriabilis*)	EC50	17,000	Kumar and Prakash (1971)
Duckweed (*Lemna minor*)	EC50	11,500	Jenner and Janssen-Mommen (1993)
Duckweed (*Lemna minor*)	NOEC	>2,400	Jenner and Janssen-Mommen (1993)
Saltwater Species			
Green alga (*Dunaliella tertiolecta*)	NOEC	104,328	Wong and Oliveira (1991)
Cyanophyceae alga (*Agemenellum quadruplicatum*)	NOEC	10,433	Wong and Oliveira (1991)
Diatom (*Chaetoceros vixvisibilis*)	NOEC	1,043	Wong and Oliveira (1991)
Dinoflagellate (*Amphidinium carterae*)	NOEC	10,433	Wong and Oliveira (1991)
Eustigmatophyceae alga (*Nannochloropsis oculata*)	NOEC	10,433	Wong and Oliveira (1991)
Prymnesiophyceae alga (*Isochrysis galbana*)	NOEC	10,433	Wong and Oliveira (1991)
Prymnesiophyceae alga (*Pavlova lutheri*)	NOEC	104,328	Wong and Oliveira (1991)

Note:

[1] EC50: 50% effective concentration; NOEC: No Observed Effect Concentration

Source: US EPA (2004)

Chronic Toxicity of Selenium to Aquatic Organisms

Chronic toxicity of selenium is largely dependent on selenium bioaccumulation via dietary exposures. Different water bodies have different types of food chains and therefore different propensities for bioaccumulation of selenium. Therefore, as discussed earlier, tissue concentrations—rather than water concentrations—provide the most reliable indicator of selenium exposure and risk to aquatic animals under different environmental conditions. Freshwater chronic tissue effect concentrations are presented in Table 3-6 and are based on endpoints such as growth, survival, and embryo larval deformities. The chronic tissue effect

concentrations for fish in Table 3-6 do not show a large variability between species; the lowest chronic value was an EC20 of 5.79 µg Se/g dw for larval deformities in rainbow trout (*O. mykiss*) (Holm, 2000 as cited by US EPA, 2004) and the highest chronic value was an EC20 of 44.57 µg Se/g dw for deformities among juvenile and adult sunfish species (Lemly, 1993a as cited by US EPA, 2004). Although the lowest genus mean chronic value (GMCV) was 9.5 µg Se/g dw whole body for a bluegill, a final chronic value (FCV) of 7.91 µg Se/g dw whole body was derived based on a study by Lemly (1993b as cited by US EPA, 2004) for over-wintering juvenile bluegill sunfish. A recent study published by US EPA (US EPA 2008b) repeated the experiment by Lemly (1993b as cited by US EPA, 2004) and examined temperature effects on the toxicity of selenium to bluegill. US EPA, (2008b) reported that the toxicity of selenium to juvenile bluegill was approximately 1.9 times less than that observed in Lemly's study. It is anticipated that the revised selenium chronic criterion will be updated with this and additional data published since 2004 for tissue and organ toxicity thresholds.

Benchmark values for chronic toxicity of selenium toward invertebrates are unavailable, to the best of our knowledge. But, based on a review of available toxicity data with clear relevance to population-level effects in invertebrates (benthic, zooplanktonic, and terrestrial invertebrates), selenium effects occurred at 1-30 µg Se/g dw (Debruyn and Chapman, 2007). This indicates a similar sensitivity in invertebrates and fish, with some invertebrates potentially being more sensitive. However, based on field observations, invertebrates appear to be more tolerant than fish and birds, with observed invertebrate tissue levels as high as 102 µg Se/g dw without any apparent adverse effects (Schuler *et al*., 1990, as cited by Debruyn and Chapman, 2007).

Aquatic birds (*e.g.*, waterfowl or shorebirds) should also be considered in an evaluation of potential impacts from selenium to aquatic organisms because these birds consume aquatic plants, invertebrates, and fish as a large portion of their diet. As with fish, chronic toxicity of selenium to aquatic birds is dependent on selenium bioaccumulation in dietary exposures. Because the embryo is the avian life stage most sensitive to selenium toxicity (Beyer *et al*., 1996), concentration thresholds in bird eggs have been examined by a number of researchers to provide a means to evaluate selenium toxicity in the field (Beyer *et al*., 1996; Ohlendorf *et al*., 2003; Fairbrother *et al*., 1999; Adams *et al*., 2003). A range of egg tissue thresholds have been proposed in the literature, including 3 mg Se/kg ww (Beyer *et al*., 1996) and 6.4-16 mg Se/kg dw (Adams *et al*., 2003; Ohlendorf *et al*., 2003), as concentrations that may be associated with embryotoxicity. Generally, these thresholds have not been used for regulatory purposes; however, recently the State of Utah has adopted the threshold range of 6.4-16 mg Se/kg dw for use in setting selenium water quality standards for the Great Salt Lake (Utah Department of Environmental Quality, 2008). Thus, when evaluating the toxicity of selenium to birds (particularly aquatic birds) it may be important to consider egg tissue thresholds as well as Eco-SSLs (discussed in the next section). The avian Eco-SSL values are derived using surrogate species and exposure models based primarily on terrestrial-feeding birds and are not meant to address aquatic-dependent wildlife.

Table 3-6
Chronic Aquatic Toxicity of Selenium in Tissue

General/Species	Chronic Value[1] (µg Se/g dw)	SMCV[2] (µg Se/g dw)	GMCV[3] (µg Se/g dw)
Brachionus sp. (rotifer)	42.36	42.36	42.36
Oncorhynchus sp. (salmonid)	5.79-19.16	9.32-12.84	10.66
Salvelinus sp. (brook trout)	12.4-13.2	12.8	12.8
Pimephales sp. (fathead minnow)	5.96-51.40	<18.21	<18.21
Catostomus sp. (flannelmouth sucker)	>10.2	>10.2	>10.2
Xyrauchen sp. (razorback sucker)	>12.9->42	>23.8	>23.8
Lepomis sp. (bluegill)	>3.74-<59.92	9.5	9.5
Lepomis sp. (bluegill)	7.91[4]		
Lepomis sp. (bluegill)	9.56-13.29 (EC10)[5] 10.16-14.02 (EC20)		
Centrarchidae sp. (9 species)	44.57		
Morone sp. (striped bass)	<14.75	<14.75	<14.75

Notes:

[1] Endpoints included are EC20 (20% effective concentration), MATC (maximum allowable toxicant concentration), NOAEC (highest no observed adverse effect concentration), and LOAEC (lowest observed adverse effect concentration).

[2] Species mean chronic values

[3] Genus mean chronic values

[4] Final chronic value for over-wintering juvenile bluegill sunfish (Lemly, 1993b)

[5] Range of chronic results for over-wintering juvenile bluegill sunfish (US EPA, 2008b)

Source: US EPA (2004), unless stated otherwise

Maier and Knight (1994, as cited by US EPA, 2004) reported that toxic threshold concentrations for selenium in water are only two to five times greater than typical background concentrations. Background concentrations of selenium in natural surface water rarely exceed 1 µg/L and average concentrations may be as low as 0.1 µg/L (Hem, 1992, as cited by Salminen *et al*., 2005). In European streams, selenium concentrations range from < 0.01 µg/L to 7.6 µg/L, with a median value of 0.34 µg/L (Salminen *et al*., 2005). The aquatic benchmark values reviewed here are generally higher than two to five times the natural background aquatic concentrations for selenium; for example, from Tables 3-1 to 3-6, the lowest GMAV of 255 µg/L (for bay scallop) and the lowest chronic benchmark of 9.5 µg/L (for bluegill) are 1.3 to 34 times the maximum (28 to 750 times the median concentration) natural background level of 7.6 µg/L (median = 0.34 µg/L) reported by Salminen *et al*. (2005).

Terrestrial Toxicity of Selenium

Selenium exists primarily as selenite and selenate in well-aerated alkaline soils. Although selenite is soluble, it can strongly adsorb to soil minerals and organic material (Tukunaga *et al*., 1997). Selenate is the most mobile selenium compound because of its high water solubility and lower affinity toward soil particles (ATSDR, 1996, as cited by US EPA, 2007a). Selenate is also more bioavailable than selenite for uptake by terrestrial organisms. However, a distinction between selenate and selenite terrestrial toxicity has not been made in US EPA's selenium Eco-SSLs, and only total selenium concentrations (in mg Se/kg dw soil) were considered.

Eco-SSLs are soil concentrations (reported as mg Se/kg dw soil) of contaminants that are presumed to provide adequate protection of ecological receptors that commonly come into contact with and/or consume biota that live in or on soil. Eco-SSLs are intended for use in screening level ecological risk assessments and are necessarily conservative, *i.e.*, over-protective. Eco-SSLs are derived separately for four groups of ecological receptors: plants, soil invertebrates, birds, and mammals. The Eco-SSL for selenium is based on an extensive terrestrial ecotoxicity data set (US EPA, 2007a). A brief review of selenium terrestrial toxicity, based on US EPA's Eco-SSL document, is provided below.

Selenium phytotoxicity occurs when selenium is taken up and incorporated into selenium analogs of essential sulfur compounds and it is generally manifested as stunted growth, chlorosis, pink leaf veins, and pink root tissue (Mikkelsen *et al*., 1989, as cited by Marschner, 1995). The selenium Eco-SSL for plants of 0.52 mg Se/kg dw in soil was derived by taking the geometric mean of eight eligible benchmark values. The eligible benchmarks included EC20s (20% Effect Concentration) and MATCs (maximum allowable toxicant concentration) for growth of various plants [Alfalfa (*Medicago sativa*), barley (*Hordeum vulgare*), Brassica (*Brassica ropa*), Raya (*Brassica juncea*), Berseem (*Trifolium alexandrinum*), and cowpea (*Vigna sinensis*)]. The EC20 and MATC values ranged from 0.1 to 1.6 mg Se/kg dw in soil.

Similarly, the selenium Eco-SSL for invertebrates of 4.1 mg Se/kg dw was derived by taking the geometric mean of three eligible benchmark values. The eligible benchmarks were EC20s for reproduction in earthworm (*Eisenia fetida*), Enchytraeidae (*Enchytraeis crypticus*), and springtail (*Folsomia candida*), and ranged from 3.4 to 4.1 mg Se/kg dw in soil.

US EPA (2007a) derived Eco-SSLs for terrestrial birds and mammals in a two-step process. First, a toxicity reference value (TRV) was derived, which is the daily dose of selenium in diet (in mg Se/kg body weight/day) that does not result in adverse effects. Second, the Eco-SSL was back-calculated for three surrogate species (dove, woodcock, and hawk) representing three different trophic levels (herbivore, insectivore, and carnivore), using the TRV and wildlife foodweb chemical exposure models (US EPA, 2003). An avian dietary TRV of 0.290 mg Se/kg bw/day was derived, based on reproductive and growth effects. Using this TRV and wildlife foodweb modeling, three separate Eco-SSLs were derived: 2.2, 1.2, and 83 mg/kg dw for the dove, woodcock, and hawk, respectively. The lowest of the three separate Eco-SSLs is used as the final avian Eco-SSL (*i.e.*, 1.2 mg Se/kg dw in soil).

The mammalian Eco-SSL was derived using a dietary TRV of 0.143 mg Se/kg bw/day based on the NOAEL and LOAEL values for reproduction and growth. Using this TRV and the wildlife foodweb exposure models for three surrogate mammals (vole, shrew, and weasel) representing a herbivore, an insectivore, and a carnivore, three separate Eco-SSLs were derived: 2.7, 0.63, and 2.8 mg Se/kg dw in soil for the vole, shrew, and weasel, respectively. Based on these values, the final Eco-SSL for mammals is 0.63 mg Se/kg dw in soil.

The Eco-SSL values are generally near background concentrations of selenium in soil. As a natural constituent of the earth's crust, selenium is ubiquitous in the environment; the average crustal selenium concentration is 0.05 to 0.09 mg Se/kg dw (Salminen *et al*., 2005). The average background concentration of selenium in US soils ranges from 0.25 to 0.53 mg Se/kg dw (Bradley *et al*., 1994; Chen *et al*., 1999; Shacklette and Boerngen, 1984) and the maximum selenium concentration in uncontaminated US soils is reported by USGS to be 4.3 mg Se/kg (Shacklette and Boerngen, 1984), *i.e.*, higher than the mammalian Eco-SSL of 0.63 mg Se/kg dw in soil. Invertebrate and avian Eco-SSL values are higher than the 95th percentile of reported background concentrations in US soils, but plants and mammalian Eco-SSLs can be well within the range of selenium soil levels measured throughout the US (US EPA, 2007a). Benchmark values at or near background do not indicate that toxicity may occur at background soil levels, but rather that benchmark development is a conservative process that likely overestimates actual ecological risk.

Ecological Effects of Anthropogenic Sources of Selenium

While several different industries may contribute to environmental selenium (*i.e.*, mining/ refining/smelting activities, agricultural runoff, animal feed and human supplements production and usage), when improperly handled, coal combustion residues (CCR) can be considered a major source of anthropogenic selenium in the environment (ATSDR, 2003). Selenium has been suggested to be the primary metal of concern in several ecological habitats affected by CCR (Rowe *et al*., 2002). Environments known to be affected by CCRs include the Martin Creek Reservoir (TX), Belews Lake (NC), the Hyco Reservoir (NC), and the D-Area Facility, Savannah River Site (SC) (Rowe *et al*., 2002). Agricultural drainage systems provide another source of selenium to the environment, which has been suggested to contribute to effects observed in aquatic birds in San Joaquin Valley, CA (Hoffman, 2002; Ohlendorf, 2002).

As discussed below, although selenium has been implicated as the most significant chemical of concern at these sites, interactions between selenium, other CCR constituents, and ecological receptors are complex. More research is needed to understand the role of selenium in causing aquatic toxicity, relative to other chemicals present at these sites. Table 3-7 presents an overview of environmental and ecological conditions at the CCR-impacted sites noted above.

Table 3-7
A Summary of Metals Concentrations in Water, Sediment, and Biota and Their Reported Adverse Effects in Belews Lake, NC, Martin Creek Reservoir, TX, D-Area Power Facility, Savannah River Site, SC, and Hyco Reservoir, NC

Sample Matrix (Concentration Units)	Sample Description/ Organism Names (Dates of Collection)	Sampled Tissue Type	As	Cd	Cr	Cu	Pb	Se	Reported Effects
Belews Lake, NC[1] (A 1564-ha cooling reservoir for a 2280-MW coal-fired power plant; received effluents from CCR basins between 1974 and 1985; effluents discharge ceased in 1985 following observations of ecological effects)									
Water (ppb)	Lake water before CCR effluent discharge		BDL	NR	NR	NR	NR	BDL	
	CCR effluent		190-253	NR	NR	NR	NR	157-218	
	Lake water (2 yr after initial discharge)		4-10 6.6	NR NR	NR NR	NR NR	NR NR	7-14 12.6	
	Lake water (5 yr after initial discharge)		4.3	NR	NR	NR	NR	9.5	
	Lake water (8 yr after initial discharge)		3.1	NR	NR	NR	NR	8.8	
	Lake water (22 yr after initial discharge, or 11 yr after final discharge)		NR	NR	NR	NR	NR	< 1	

Table 3-7 (continued)
A Summary of Metals Concentrations in Water, Sediment, and Biota and Their Reported Adverse Effects in Belews Lake, NC, Martin Creek Reservoir, TX, D-Area Power Facility, Savannah River Site, SC, and Hyco Reservoir, NC

Sample Matrix (Concentration Units)	Sample Description/ Organism Names (Dates of Collection)	Sampled Tissue Type	As	Cd	Cr	Cu	Pb	Se	Reported Effects
Sediment (ppm DM)	2 yr after initial discharge		31.2-59.8	NR	NR	NR	NR	6.08-8.93	
	22 yr after initial discharge (or 11 yr after final discharge)		NR	NR	NR	NR	NR	1-4	
Invertebrates (ppm)	Plankton (in 1977)	(DM)	3.1-11.3	NR	NR	NR	NR	41.3-97.0	
	Mayfly (in 1979)	(WM)	3.05 NR	NR NR	NR NR	NR NR	NR NR	8.36 13.6	
Fish (ppm)	Catfish Sunfish (in 1977, 3 yr after initial discharge)	Skeletal muscle (WM) Skeletal muscle (WM)	< 0.1-0.34 < 0.1-2.65	NR NR	0.21-0.27 0.05-1.69	NR NR	NR NR	7.96-11.3 10.6-22.3	
	Green sunfish (3 yr after initial discharge)	Skeletal muscle (WM)	NR	NR	NR	NR	NR	12.9-21.4	Decreased hematocrit, increased condition factor and hepatopancreas-to-bodyweight ratio due to edema, histological abnormalities (liver, kidney, gill, heart, ovary)

Table 3-7 (continued)
A Summary of Metals Concentrations in Water, Sediment, and Biota and Their Reported Adverse Effects in Belews Lake, NC, Martin Creek Reservoir, TX, D-Area Power Facility, Savannah River Site, SC, and Hyco Reservoir, NC

Sample Matrix (Concentration Units)	Sample Description/ Organism Names (Dates of Collection)	Sampled Tissue Type	As	Cd	Cr	Cu	Pb	Se	Reported Effects
	Bluegill fingerlings caged for 8 d in lake receiving CCR (in 1979)	Muscle (WM) Viscera (WM)	<0.01-0.03 < 0.02-0.20	NR NR	NR NR	NR NR	NR NR	0.6-3.4 3.6-7.5	Erratic swimming, exopthalmia, abdominal distention
	Juvenile Bluegills fed invertebrates collected from CCR-contaminated lake for 44 d (in 1979)	Muscle (WM) Liver (WM)	NR NR	NR NR	NR NR	NR NR	NR NR	7.503-7.936 69-86	Edema, food avoidance, histopathological changes
Birds (ppm)	American coot in 1996 (22 yr after initial discharge, 11 yr after final discharge)	Eggs (estimated by author from liver concentrations) Liver (back-calculated by author from egg concentration estimates)	NR NR	NR NR	NR NR	NR NR	NR NR	2-5 6-15	
Martin Creek Reservoir, TX[2] **(A 2000-ha cooling reservoir for a coal-fired power plant; received CCR effluents from two settling ponds between September 1978 and May 1979; effluents discharge ceased after observations of fish kills)**									
Water (ppb)	CCR ponds discharging into reservoir (in 1980 and 1982)		NR	NR	NR	NR	NR	2,200-2,700	
Invertebrates (ppm)	Mayfly (in 1980 and 1982)	(DM)	NR	NR	NR	NR	NR	14.8	

Table 3-7 (continued)
A Summary of Metals Concentrations in Water, Sediment, and Biota and Their Reported Adverse Effects in Belews Lake, NC, Martin Creek Reservoir, TX, D-Area Power Facility, Savannah River Site, SC, and Hyco Reservoir, NC

Sample Matrix (Concentration Units)	Sample Description/ Organism Names (Dates of Collection)	Sampled Tissue Type	As	Cd	Cr	Cu	Pb	Se	Reported Effects
Fish (ppm)	Spotted gar (in 1980 and 1982)	Muscle (WM)	NR	NR	NR	NR	NR	2.0-3.0	
	Sunfish (in 1980 and 1982)	(DM)	NR	NR	NR	NR	NR	16.9	
	Largemouth bass (in 1980 and 1982)	(DM)	NR	NR	NR	NR	NR	39	
	Field collected adult Largemouth bass (in 1980 and 1982)	Muscle (WM)	NR	NR	NR	NR	NR	3.8-8.3 [3]	Reduced reproductive success and population fluctuations
	Field collected adult Channel catfish (in 1980 and 1982)	Muscle (WM)	NR	NR	NR	NR	NR	2.7-4.6 [3]	Reduced adult biomass
	Field collected adult: Gizzard shad Common carp Long ear sunfish Bluegill Red ear sunfish (in 1980 and 1982)	Muscle (WM)	 NR NR NR NR NR	 NR NR NR NR NR	 NR NR NR NR NR	 NR NR NR NR NR	 NR NR NR NR NR	 2.9-7.3 [3] 3.6-9.1 [3] 5.1 3.4-6.8 [3] 4.4-5.6 [3]	 Population decline Population decline Population decline Population decline Population decline

Table 3-7 (continued)
A Summary of Metals Concentrations in Water, Sediment, and Biota and Their Reported Adverse Effects in Belews Lake, NC, Martin Creek Reservoir, TX, D-Area Power Facility, Savannah River Site, SC, and Hyco Reservoir, NC

Sample Matrix (Concentration Units)	Sample Description/ Organism Names (Dates of Collection)	Sampled Tissue Type	As	Cd	Cr	Cu	Pb	Se	Reported Effects
	Black crappie (in 1980 and 1982)	(WM)	NR	NR	NR	NR	NR	5.4-6.8	
	Gizzard shad (in 1980 and 1982)	(DM)	NR	NR	NR	NR	NR	32.3	
Birds (ppm)	Barn swallow (in 1980 and 1982)	Eggs (DM) Liver and kidney (DM)	NR NR	NR NR	NR NR	NR NR	NR NR	2.8-3.3 14-14.7	
	Red wing blackbird (in 1980 and 1982)	Kidney (DM) Stomach contents (DM) Eggs (DM)	NR NR NR	NR NR NR	NR NR NR	NR NR NR	NR NR NR	33.1 1.3 11.1	Reduced hatching success
D-Area Power Facility, Savannah River Site, SC[4] **[US Department of Energy's Savannah River Site; disposal system comprising settling basins, a swamp, and Beaver Dam Creek (a Savannah River tributary) for a 70-MW coal-fired power plant; likely the most studied aquatic CCR site]**									
Water (ppb)	Multiple portions of drainage system (1973-1979)		58-100	100-123	160-200	390-660	NR	100-110	
	Secondary settling basin, drainage swamp, and swamp outflow combined (in 1981-1982)		46	0.3	0.4	2.6	NR	NR	

Table 3-7 (continued)
A Summary of Metals Concentrations in Water, Sediment, and Biota and Their Reported Adverse Effects in Belews Lake, NC, Martin Creek Reservoir, TX, D-Area Power Facility, Savannah River Site, SC, and Hyco Reservoir, NC

Sample Matrix (Concentration Units)	Sample Description/ Organism Names (Dates of Collection)	Sampled Tissue Type	As	Cd	Cr	Cu	Pb	Se	Reported Effects
	Beaver Dam Creek, 0.3 to 1 km below drainage swamp outflow (in 1981-1982)		2.4	0.2	0.4	20	NR	NR	
	Primary settling basin (in 1980s)		17.17	0.11	0.44	2.53	0.08	7	
Suspended solids (ppm DM)	Secondary settling basin, drainage swamp, and swamp outflow combined (in 1981-1982)		762	9.6	73	207	NR	NR	
	Beaver Dam Creek, 0.3 to 1 km below drainage swamp outflow (in 1981-1982)		28	0.9	52	406	NR	NR	
	Beaver Dam Creek (in 1970s)		NR	1.9	70	149	80	NR	
Sediment (ppm DM)	Multiple portions of drainage system (prior to 1976; ppm WM)		19.7-47.9	1.7	38-38.4	52-81	NR	5.6-6.1	

Table 3-7 (continued)
A Summary of Metals Concentrations in Water, Sediment, and Biota and Their Reported Adverse Effects in Belews Lake, NC, Martin Creek Reservoir, TX, D-Area Power Facility, Savannah River Site, SC, and Hyco Reservoir, NC

Sample Matrix (Concentration Units)	Sample Description/ Organism Names (Dates of Collection)	Sampled Tissue Type	As	Cd	Cr	Cu	Pb	Se	Reported Effects
	Outflow from drainage swamp		0.95-1.69 2.48	0.05-0.06 0.12	0.57-0.62 0.77	0.65-0.96 2.09	NR NR	0.15-0.19 0.24	
	Primary settling basin (in 1995-1996)		70.8	0.57	NR	71.8	45.2	6.21	
	Drainage swamp (in 1995-1996)		116.6 28.94	2.32 1.38	NR 22.04	147.5 43.5	66.2 NR	7.78 7.11	
	Terrestrial margins of primary settling basin (in 1990s)		39.638	0.252	10.869	18.386	6.457	4.383	
	Secondary settling basin (in 1990s)		49.39	0.72	23.85	84.72	NR	6.11	
Plants (ppm)	Six species (in 1970s)	Pooled (WM)	4.2-5.3	0.9-1.5	2.9-5.7	7.2-14	NR	1.8-5	
	Five species (in 1970s)	Pooled (WM)	NR	0.4-4.7	0.9-4.2	2-34	NR	1.8-5.7	
	Algae (in 1970s)	(WM)	NR	1.3-1.9	4-4.5	7-9.9	NR	1.3-1.4	

Table 3-7 (continued)
A Summary of Metals Concentrations in Water, Sediment, and Biota and Their Reported Adverse Effects in Belews Lake, NC, Martin Creek Reservoir, TX, D-Area Power Facility, Savannah River Site, SC, and Hyco Reservoir, NC

Sample Matrix (Concentration Units)	Sample Description/ Organism Names (Dates of Collection)	Sampled Tissue Type	As	Cd	Cr	Cu	Pb	Se	Reported Effects
Invertebrates (ppm)	Chironomids (in 1970s)	(WM)	NR	1.2	38	50	NR	0.7	
	Field collected Chironomids (in 1973-1977)	Whole body (WM)	2.9 1.93	NR 1.15	NR 38.27	56 50	NR NR	NR 0.7	Decreased population density Decreased population density
	Field collected (in 1970s)	Odonates (WM)	NR	1-1.2	3.4-4.5	20-27	NR	2.5-2.6	
	Field collected Odonates (in 1973-1977)	Muscles (WM)	5.2-6.2 6.05 1.35	NR 1.2 1	NR 3.43 4.49	33.8-39.1 26.84 20	NR NR NR	4-4.2 2.48 2.5	Decreased population density Decreased population density Decreased population density
	Multiple species (insects, mollusks, and crustaceans) (in 1990s)	Pooled (WM)	2.1-60	2.5-4	3.5-9.7	31-67	NR	2.6-6.5	
	Asiatic clams (in 1990s)	Flesh (DM)	13.22	4.02	5.63	64.87	NR	8.69	
	Crayfish (in 1990s)	Whole body (DM)	8.71	2.78	2.46	158.52	NR	14.92	

Table 3-7 (continued)
A Summary of Metals Concentrations in Water, Sediment, and Biota and Their Reported Adverse Effects in Belews Lake, NC, Martin Creek Reservoir, TX, D-Area Power Facility, Savannah River Site, SC, and Hyco Reservoir, NC

Sample Matrix (Concentration Units)	Sample Description/ Organism Names (Dates of Collection)	Sampled Tissue Type	As	Cd	Cr	Cu	Pb	Se	Reported Effects
	Crayfish (in 1970s)	(WM)	NR	16	7.7	19	NR	7.2	
	Field collected Crayfish (in 1973-1977)	Abdominal muscle (WM)	2.1 1.36	NR 15.63	NR 7.66	26.3 19.31	NR NR	4.4 7.2	Decreased population density Decreased population density
	Field collected Gastropod (in 1973-1977)	Whole body (WM)	18.2	NR	NR	30.3	NR	1.2	Decreased population density
Fish (ppm)	Mosquito fish (in 1973-1977)	Caudal peduncle muscle (WM)	0.5 2	1.3 NR	2.76 NR	8.45 11.5	NR NR	9.4 9.2	Decreased population density
	Mosquito fish (in 1997)	Whole body (DM)	0.5 2.89	1.3 0.32	2.8 1.56	6.9 4.97	NR NR	9.4 14.28	
	Bluegill (in 1997)	Whole body (DM)	2.61	0.75	2.38	1.02	NR	19.52	
	Largemouth bass (in 1997)	Whole body (DM)	1.92	0.31	1.27	4.2	NR	18.32	
Amphibians (ppm)	Frog larvae (in 1970s)	(WM)	NR	0.8	0.6	13	NR	6.6	

Table 3-7 (continued)
A Summary of Metals Concentrations in Water, Sediment, and Biota and Their Reported Adverse Effects in Belews Lake, NC, Martin Creek Reservoir, TX, D-Area Power Facility, Savannah River Site, SC, and Hyco Reservoir, NC

Sample Matrix (Concentration Units)	Sample Description/ Organism Names (Dates of Collection)	Sampled Tissue Type	As	Cd	Cr	Cu	Pb	Se	Reported Effects
	Bullfrog larvae raised in CCR settling basin until 60 d old prior to exposure to predators in mesocosms		NR	NR	NR	NR	NR	NR	Increased susceptibility to predation
	Bullfrogs, recent metamorphs (in 1997)	Whole body (DM)	15.55	0.8	1.58	13.79	NR	26.85	
	Adult Southern toads (in 1990s)	Whole body (DM)	1.58	0.27	1.87	29.5	0.7	17.4	
	Southern toad larvae hatched and raised in settling basin through metamorphosis (in 1990s)		NR	NR	NR	NR	NR	NR	100% mortality associated with severe reductions in resource (periphyton) abundance; potential for contaminated site to act as a sink habitat for local populations
	Adult Green tree frogs (in 1997)	Whole body (DM)	1.01	0.28	7.86	19.82	NR	9.82	

Table 3-7 (continued)
A Summary of Metals Concentrations in Water, Sediment, and Biota and Their Reported Adverse Effects in Belews Lake, NC, Martin Creek Reservoir, TX, D-Area Power Facility, Savannah River Site, SC, and Hyco Reservoir, NC

Sample Matrix (Concentration Units)	Sample Description/ Organism Names (Dates of Collection)	Sampled Tissue Type	As	Cd	Cr	Cu	Pb	Se	Reported Effects
Reptiles (ppm)	Adult Banded water snake (in 1997)	Liver (DM)	134.3	0.5	2	82.7	NR	141.9	
	Adult Softshell turtle	Muscle (DM)	18.3	4.9	2.2	41.4	0.7	21.9	
		Slider turtle, adult, liver (DM)	9.56	3.57	6.19	102.23	NR	37.18	
	Adult Banded water snake fed fish collected from CCR-contaminated site for 13.5 mo. (in 1990s)	Liver (DM) Kidney (DM) Gonad (DM)	0.86 0.35 0.15	1.07 0.44 BDL	NR NR NR	35.07 7.78 7.55	NR NR NR	22.63 23.2 15.34	
	Adult Banded water snake fed fish collected from CCR-contaminated site for 2 yr. (in 1990s)	Liver (DM) Kidney (DM) Gonad (DM)	1.851-2.010 0.817-1.055 0.335-0.520	1.625-1.718 0.234-0.573 0.055-0.059	NR NR NR	27.822-60.475 6.475-6.777 5.299-5.570	NR NR NR	24.076-24.220 25.379-32.036 17.642-19.060	

Table 3-7 (continued)
A Summary of Metals Concentrations in Water, Sediment, and Biota and Their Reported Adverse Effects in Belews Lake, NC, Martin Creek Reservoir, TX, D-Area Power Facility, Savannah River Site, SC, and Hyco Reservoir, NC

Sample Matrix (Concentration Units)	Sample Description/ Organism Names (Dates of Collection)	Sampled Tissue Type	As	Cd	Cr	Cu	Pb	Se	Reported Effects
Hyco Reservoir, NC[5] **(A 1764-ha cooling reservoir for a coal-fired power plant; received effluents from CCR basins and heated water discharge; observations of fish declines and fish kill in 1980 prompted investigations)**									
Sediment (ppm DM)	Cooling reservoir receiving CCR effluent (in 1977-1978)		1.8-13.3	NR	24-197	15-104	NR	0.68-5.50	
Fish (ppm)	Bluegill (in 1980s)	Carcass (WM)	0.05-0.11	0.007-0.01	NR	0.36-0.99	0.05-0.26	6.90-7.20	Reproductive failure
	Bluegill larvae derived from crosses of adults from CCR-contaminated site (in 1980s)	Whole body (WM)	NR	NR	NR	NR	NR	28.2	Edema and reduced larval survival

Notes:

ha: hectare; MW: Megawatt; ppb: parts per billion; ppm: parts per million; NR: Not Reported; BDL: Below Detection Level; WM: Weight Mass; DM: Dry Mass.

[1] Compiled by Rowe et al. (2002) from Cumbie (1978), Sorenson et al. (1984); Finley (1985), Olmsted et al. (1986), and Lemly (1997).

[2] Compiled by Rowe et al. (2002) from Garrett and Inman (1984), USDI (1988), and King et al. (1994).

[3] Range in concentrations reflects values obtained one year following an eight-month. period of CCR discharge into reservoir (high values; 1980) and values obtained two years later (low values; 1982) to examine recovery of the system.

[4] Compiled by Rowe et al. (2002) from Cherry (1976 and 1979), Cherry et al. (1976, 1979a,b), Cherry and Guthrie (1977), Guthrie and Cherry (1976, 1979), Evans and Giesy (1978), Alberts et al. (1985), McCloskey et al. (1995), McCloskey and Newman (1995), Rowe et al. (1996), Raimondo et al. (1998), Hopkins et al. (1998, 1999a, 2001a, 2002a), and Nagle et al. (2001).

[5] Compiled by Rowe et al. (2002) from CPL (1979) and Gillespie and Baumann (1986).

[Source: Data presented in this table are extracted from Tables III, IV, VI, and VII in Rowe et al. (2002)]

Shortly after the Martin Creek Reservoir received effluents from two fly ash settling ponds (belonging to a coal-fired power plant) between September 1978 and May 1979, fish kills in the reservoir were observed (Garrett and Inman, 1984, as cited by Rowe *et al*., 2002). Studies of the Martin Creek system demonstrated severe and widespread changes in tissue morphology which appeared to be primarily related to availability and accumulation of high concentrations of Se derived from CCR inputs (Rowe *et al*., 2002; Sorensen *et al*., 1988). Hyco Reservoir, a cooling reservoir, received effluents from coal ash basins, and fish declines and fish kills were observed in the fall of 1980 (CPL, 1981, as cited by Rowe *et al.*, 2002). Selenium concentrations were the focus of these investigations as other contaminants (metals and organics) were similar to normal background concentrations (Rowe *et al*., 2002; Baumann and Gillespie, 1986). The Savannah River site is a CCR disposal system associated with a United States Department of Energy (US DOE) Power Facility (settling basins, drainage swamp, and surface water discharge to a tributary of the Savannah River). A number of studies associated with the Savannah River site have reported elevated levels of metals, including selenium, and ecological effects in amphibians, reptiles, fish, and invertebrates (Rowe *et al*., 1996, 2001; Hopkins and colleagues, 1998-2003, as cited by Rowe *et al*., 2002). Although arsenic and selenium concentrations were found to be elevated, many metals were found to accumulate in organisms and may have contributed to the adverse ecological outcomes (Rowe *et al*., 2002). Belews Lake, a cooling reservoir constructed in 1970, received CCR effluents beginning in 1974. The CCR effluent discharge in Belews Lake stopped in 1985 following observations of fish declines in 1976 and subsequent community level changes. Selenium concentrations were found to correlate with developmental abnormalities in fish (Lemly, 1985, 1993, 1997, 2002; Rowe *et al*., 2002). Although selenium was suggested to play a role in the effects observed at these sites, the complex chemical nature of CCR suggests that in many systems, a single contaminant such as Se may not be responsible for biological changes (Rowe *et al*., 2002). Rather, the combined effects of multiple accumulated elements may lead to numerous changes in individuals that could compromise individual fitness or health (Rowe *et al.*, 2001, 2002).

As seen in Martin Creek, the Hyco Reservoir, and the Belews Lake systems, the most obvious CCR-related effects were declines in fish populations. These fish population declines were associated with elevated concentrations of Se, which can be toxic at certain concentrations to sensitive species and at certain life stages. Resident fish populations following the end of CCR release (in the Martin Creek and Belews Lake) took several years to recover, suggesting that contaminants can persist in some aquatic systems (Rowe *et al*., 2002). Besides fish population declines, maternal transfer of selenium to eggs of fish, turtles, alligators, and birds have also been observed, suggesting trans-generational effects. Because CCRs are more highly enriched in selenium compared to other metals, selenium has been implicated as a potential contaminant of concern. However, as discussed earlier, measured dissolved selenium concentrations do not necessarily indicate the potential for chronic toxicity because it is presently uncertain how to relate water concentrations to food chain uptake (Chapman, 2009). For example, chronic selenium toxicity is hypothesized to have caused severe declines in the Hyco Reservoir fish populations, but there was no apparent effect on the adjacent Mayo Reservoir with similar selenium inputs (Chapman, 2009). The contribution of selenium (relative to other metals) to the

environmental effects of CCR requires further evaluation due to the complexity of metal interactions, site-specific conditions, and species sensitivity differences.

Agricultural drainage systems provide another source of selenium to the environment (unrelated to CCR releases) (Hoffman, 2002; Ohlendorf, 2002). Based on a speciation study, proteinaceous selenomethionine from agricultural drainage was suggested to be the chemical species responsible for selenium transfer in the food chain resulting in adverse effects on aquatic feeding birds in the San Joaquin Valley (Hoffman, 2002; Ohlendorf, 2002; Spallholz and Hoffman, 2002).

Selenium Regulatory Criteria and Screening Guideline Values

The criteria and screening values provided in Table 3-8 incorporate different trophic levels and target the protection of ecosystems in their entirety (*e.g.*, the aquatic or terrestrial environment). Generally, these values are derived to provide protection to a majority of aquatic or terrestrial organisms, populations, communities and/or ecological functions. If federal- or state-listed threatened or endangered species or commercially important species are present, then species-specific toxic benchmark values (such as those provided in Tables 3-2 to 3-6) can be used to evaluate potential risks to these species at contaminated sites.

Table 3-8 lists the available AWQC for the protection of aquatic life for selenium, along with other available selenium screening values for the protection of aquatic and terrestrial wildlife. Ecological screening values and regulatory criteria (proposed or otherwise) are based on extensive reviews of the literature (*i.e.*, Eco-SSL and AWQC derivation processes). To determine the potential for ecological risk from selenium exposure, the criteria values listed in Table 3-8 are typically compared to selenium concentrations in site soil, surface water, or fish tissue.

Table 3-8
Selenium Regulatory Criteria and Screening Guideline Values for the Protection of Aquatic and Terrestrial Wildlife

Regulatory Agency	Criterion	Concentration	Reference(s)
	Surface Water	**(µg Se/L)**	
US EPA	AWQC:		US EPA (2009b)
	Freshwater Chronic	5.0	
	Saltwater Chronic	71.0	
	Saltwater Acute	290.0	

Table 3-8 (continued)
Selenium Regulatory Criteria and Screening Guideline Values for the Protection of Aquatic and Terrestrial Wildlife

Regulatory Agency	Criterion	Concentration	Reference(s)
	Surface Water	**(µg Se/L)**	
US EPA	Draft AWQC:		US EPA (2004)
	Freshwater Acute Selenite	258.0	
	Freshwater Acute Selenate	417.0	
	Saltwater Acute Selenite	127.0	
US EPA, Region IV	Screening Values for Hazardous Waste Sites:		US EPA, Region IV (2001)
	Acute	20.0	
	Chronic	5.0	
US EPA, Region V	Ecological Screening Level	5.0	US EPA, Region V (2003)
US EPA, Region VI	Screening Benchmarks:		TNRC (2001)
	Freshwater	5.0	
	Marine	136.0	
Canadian Environmental Quality Guideline	Freshwater Aquatic Life	1.0	CCME (2002)
US Department Of Energy	Screening Benchmarks[1]:		ORNL (1996)
	Aquatic Plants	100.0	
	Daphnids	91.7	
	Fish	88.3	
	Soil	**(mg Se/kg)**	
Literature	Average Background Soil Concentrations in the US	0.25-0.53	Bradley *et al.* (1994), Chen *et al.* (1999), Shacklette and Boerngen (1984)
US EPA	Eco-SSLs:		US EPA (2007a)
	Plants	0.52	
	Invertebrates	4.10	
	Birds	1.20	
	Mammals	0.63	

Table 3-8 (continued)
Selenium Regulatory Criteria and Screening Guideline Values for the Protection of Aquatic and Terrestrial Wildlife

Regulatory Agency	Criterion	Concentration	Reference(s)
	Surface Water	**(µg Se/L)**	
Oak Ridge National Laboratory (ORNL)	Screening Benchmarks:		
	Invertebrates	70.0	Efroymson *et al.* (1997a)
	Microbes	100.0	Efroymson *et al.* (1997a)
	Plants	1.0	Efroymson *et al.* (1997b)
US EPA, Region IV	Screening Value for Hazardous Waste Sites	0.81	US EPA, Region VI (2001)
Canadian Environmental Quality Guideline	Screening Value	1.0	CCME (2002)
US EPA, Region V	Ecological Screening Levels	0.0276[2]	US EPA, Region V (2003)
US EPA, Region VI	Screening Benchmarks:		TNRC (2001)
	Earthworms	70.0	
	Plants	1.0	
Dutch Ministry Standards	Screening Levels:		Swartjes (1999)
	Intervention Value[3]	5.0	
	Target Value[4]	0.7	
	Tissue	**(mg Se/kg)**	
US EPA	Fish tissue	7.91 (dry weight)[5]	US EPA (2004)
Literature	Avian Egg	3 (wet-weight)[1] 6.4-16 (dry weight)	Beyer *et al.* (1996), Ohlendorf *et al.* (2003), Adams *et al.* (2003)
	Avian Liver	3 (wet-weight)[1]	

Notes:

[1] Based on lowest acceptable chronic value (LCV)
[2] Based on exposure of a small terrestrial mammal (i.e., the masked shrew, Sorex cinerus)
[3] The Intervention Value is the concentration expected to be hazardous to 50% of the species in the ecosystem.
[4] Target Values represent the environmental exposures associated with negligible risk for ecosystems. These values are assumed to be 1% of the Maximal Permissible Risk (MPR) level for ecosystems, where MPR is the concentration expected to be hazardous for 5% of the species in the ecosystem, or the 95% protection level.
[5] Tissue concentration in µg Se/g dry wt

Lower screening values in Table 3-8 generally consider long-term exposure scenarios and chronic effects, and, therefore, provide a more conservative estimate of levels associated with ecological protection. Additionally, screening criteria are typically based on the most sensitive benchmark value (*e.g.*, NOAEL, LOAEL, or EC20) and include additional safety factors. For example, the Canadian Environmental Quality Guideline of 1.0 μg/L for freshwater aquatic life is intended to be protective of all life stages during an indefinite exposure to selenium in water; it is derived by multiplying the available LOAEL by a safety factor of 0.1 (CCME, 2002).

The Draft AWQC chronic criterion for selenium is based on tissue residue to take into account the importance of dietary exposure to higher organisms in the food chain. Several concerns regarding the adequacy and/or conservatism of the chronic criterion of 7.91 μg Se/g dw, based on the tissue concentration of a warm-water fish (bluegill), has been raised for the protection of invertebrates, birds, and other vertebrates. It should be noted that a planned revision of the selenium criterion is anticipated in 2010 and this may result in a change to the draft value of 7.91 μg Se/g dw. Chapman (2007) reviewed reproductive effect studies with cold-water fish species, including trout (cutthroat, brook, and rainbow), white sucker, and northern pike and found them to be more tolerant to dietary uptake of selenium than warm-water fish species. Consequently, the draft selenium tissue criterion is expected to provide a conservative level of protection for cold-water fish. Based on laboratory results, sub-lethal effects of selenium in invertebrates occurred at 1 to 30 μg Se/g dw in invertebrate tissue, but in the field, invertebrates appeared to be much more tolerant (Debruyn and Chapman, 2007).

It is apparent from Table 3-8 that different screening values are recommended for different conditions and risk targets, such as freshwater *vs.* saltwater environments, and acute *vs.* chronic effects. Therefore, a proper application of a criterion requires adequate understanding of the underlying assumptions regarding the types of organisms, endpoints, and levels of protection desired.

Similar to single species benchmarks, the respective screening levels presented in Table 3-8 are, overall, higher than the natural background levels of selenium in surface water and at or above the natural background levels of selenium in surface soils. The aquatic screening levels (in μg/L) are 3 to 1,230 times higher (320 times on average) than the typical selenium background levels in surface waters (based on a mean of 0.34 μg/L from Salminen *et al*. [2005]), and the soil screening levels are 0.05 to 200 times higher (31 times on average) than typical selenium background levels in surface soils (based on the upper range of the average in the US soils of 0.53 μg/kg dw, as described above). Therefore, ecological risks due to selenium are unlikely in surface waters and soils that receive little or no anthropogenic selenium. The margins of exposure between some of the selenium benchmarks and background selenium concentrations are relatively small and in some cases the background values are above the benchmarks. In these cases, evaluation of excess selenium concentrations may require further refinement in exposure and effects assessments. Because of the complexity of selenium interactions within the food web, it may be important to evaluate site-specific biogeochemistry, consider species sensitivity distributions, and conduct wildlife surveys to provide more information on the ecosystem. Data from these studies/surveys may provide more insight into the condition of an ecosystem than

relying on comparisons with regulatory criteria that are not representative of site-specific conditions.

Ecological Benchmark Toolbox

Government and private websites and reports provide useful information on selenium ecotoxicity and ecological risk assessment. The list below presents some key resources.

Aquatic Life Criteria for Selenium (US EPA, 2008a)
Website: http://www.epa.gov/waterscience/criteria/selenium/

This website provides draft criteria for selenium and new information on issues in criteria development for selenium.

Ecological Benchmark Tool (Univ. of Tenn, 2007)
Website: http://rais.ornl.gov/tools/eco_search.php

This website provides a searchable database with a comprehensive set of ecotoxicological screening benchmarks for surface water, sediment, and surface soil applicable to a range of aquatic organisms, soil invertebrates, and terrestrial plants. Also provided are the links to supporting technical reports from which the benchmarks were obtained.

The ECOTOX Database (US EPA, 2007b)
Website: http://cfpub.epa.gov/ecotox/quick_query.htm

This searchable database provides aquatic and terrestrial life toxicity data and the associated primary literature references, and can be searched by chemical name.

Ecological Risk Analysis: Guidance, Tools, and Applications (ORNL, 2003)
Website: http://www.esd.ornl.gov/programs/ecorisk/contaminated_sites.html

This page contains information that can be used to conduct screening and baseline ecological risk assessments at hazardous waste sites.

Cleanup Levels For Hazardous Waste Sites (Anon., 2001)
Website: http://cleanuplevels.com/cleanup.htm

This private website is a list of primary government sources and their Internet links for cleanup and screening levels at hazardous waste sites.

4
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