

936 Agency for Toxic Substances and Disease Registry (ATSDR)
toxicological profile for Selenium

<http://www.atsdr.cdc.gov/toxprofiles/tp92.pdf>

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Summary of Health Effects

As an essential trace element in humans and animals, selenium is a biologically active part of a number of important proteins, particularly enzymes involved in antioxidant defense mechanisms (e.g., glutathione peroxidases), thyroid hormone metabolism (e.g., deiodinase enzymes), and redox control of intracellular reactions (e.g., thioredoxin reductase). Depending upon the level of intake, selenium can have nutritional or possibly toxic effects. Most people in the United States are unlikely to suffer from selenium deficiency. Although excessive intake of selenium can cause adverse health effects, these are generally observed at doses more than 5 times greater than the Recommended Dietary Allowance (RDA).

The current RDA for selenium, established by the Food and Nutrition Board of the National Research Council (National Academy of Sciences), is 55 µg/day for male and female adults (approximately 0.8 µg/kg/day). This recommendation represents a decrease from the previous RDA of 70 µg/day for males; 55 µg/day was already the RDA for females. The current NAS Tolerable Upper Intake Level (UL) for selenium is 400 µg/day for adults (approximately 5.7 µg/kg/day). At the time that the RDA was in the process of being reevaluated (i.e., late 1990s), selenium was found to have entered the environment from old mining operations in some northwestern U.S. locations. This resulted in public concern about the potential effects of selenium on livestock grazing in the vicinity, and ultimately possible effects in humans consuming food products from plants and animals raised in those areas. The combination of the increased concern regarding selenium toxicity and the reduction in the selenium RDA indicated to ATSDR that an Agency reevaluation of selenium from a toxicological perspective is warranted; the previous version of the ATSDR Toxicological Profile for Selenium was published in 1996.

Although selenium deficiency is not a health issue in the United States, it has been associated with two endemic diseases found in selenium-poor regions of China: a cardiovascular condition known as Keshan Disease and an osteoarthropathy called Kashin-Beck Disease. Keshan Disease is a cardiomyopathy characterized by cardiac enlargement, abnormal ECG patterns, cardiogenic shock, and congestive heart failure, with multifocal necrosis of the myocardium. The disease is reported to occur primarily in children and women of child-bearing age and has been successfully treated by selenium supplementation; however, a low incidence of cases persisting after selenium supplementation suggests that there may be other contributing factors. The evidence for the involvement of selenium in Kashin-Beck disease is less clear than for its involvement in Keshan disease. Kashin-Beck Disease is characterized by atrophy, degeneration, and necrosis of cartilage tissue, and occurs primarily in children between the ages of 5 and 13 years; it also has been successfully treated with selenium supplements. Chronically ill people and older people have been shown to have lower organ concentrations of selenium than healthy individuals, but it is not clear if this is a cause or consequence of aging or illness.

Relatively little information is available on health effects of elevated inhalation levels of selenium. The primary target organ in humans and laboratory animals in cases of acute, high-level inhalation exposure to selenium dusts or fumes is the lung, with cardiovascular, hepatic, nervous, and renal involvement as well. Lesser effects are observed in other organs/organ systems. Workers acutely exposed to high concentrations of elemental selenium dust have reported stomach pain and headaches, whereas workers briefly exposed to high levels of selenium dioxide dust experienced respiratory symptoms such as pulmonary edema, bronchial spasms, symptoms of asphyxiation and persistent bronchitis, elevated pulse rates, lowered blood pressure, vomiting, nausea, and irritability. No information is available on health effects in humans or laboratory animals from intermediate-duration (up to 1 year) inhalation exposure to selenium or selenium compounds. Regarding chronic inhalation exposure, several occupational studies describe respiratory effects such as irritation of the nose, respiratory tract, and lungs, bronchial spasms, and coughing following exposure to selenium dioxide or elemental selenium as dust. Respiratory symptoms similar to those reported for occupationally-exposed humans have been seen in animals inhaling high doses of elemental selenium fumes or dust, and studies of animals with acute inhalation exposure to hydrogen selenide or elemental selenium fumes or dust have reported hepatocellular degeneration and atrophy of the liver.

Acute oral exposure to extremely high levels of selenium (e.g., several thousand times more than normal daily intake) produces nausea, vomiting, and diarrhea in both humans and laboratory animals. Acute oral exposure of humans to selenium has occasionally caused cardiovascular symptoms, such as tachycardia, but no electrocardiographic abnormalities were found in individuals from a human population chronically exposed to selenium. In laboratory animals, acute- and intermediate-duration oral exposure to very large amounts of selenium (approximately 100 times normal human intake) has produced myocardial degeneration in laboratory animals.

Chronic oral intake of very high levels of selenium (10 –20 times more than normal) can produce selenosis in humans, the major effects of which are dermal and neurological. As shown by affected populations in China, chronic dietary exposure to these excess levels of selenium has caused diseased nails and skin and hair loss, as well neurological problems, including unsteady gait and paralysis. Additional information on selenosis is summarized in the following subsection of this chapter. In contrast, studies of people living in areas of naturally occurring high selenium concentrations in the United States have not revealed adverse health effects in those populations. This difference may result from a lower (~2-fold) selenium exposure in the U.S. population compared to the Chinese population, as well as a better balanced, higher protein diet in the United States, which could lead to reduced toxicity of selenium through interactions with dietary components.

Intermediate and chronic oral exposure of livestock to high levels of dietary selenium compounds also produces dermal and neurological effects. Studies in rats and other laboratory animals with high selenium tissue concentrations demonstrate that many organ systems retain selenium and are affected. The primary adverse effects in laboratory animals exposed to inorganic selenium salts or to selenium-containing amino acids are cardiovascular, gastrointestinal, hematological, hepatic, dermal, immunological, neurological, and reproductive, although doses causing these effects are generally at least 5 times higher than normal daily selenium intake. A condition (syndrome) referred to as “blind staggers” has been repeatedly observed in cattle feeding off vegetation in areas with high selenium content in the soil. However, the neurological effects have not been replicated in experimentally-exposed cattle receiving doses of selenium sufficient to induce hoof lesions, and thus, the neurological signs associated with “blind staggers” may be due to other compounds found within this vegetation.

Some evidence for effects on the endocrine system has also been found following long-term oral exposure to elevated levels of dietary selenium in humans and rats. In humans, blood levels of thyroid T3 hormone (triiodothyronine) decreased in response to increased dietary selenium for durations of 3 months and longer at intakes several times higher than normal intake, although the hormone levels remained within the normal range. In rats, type-I-deiodinase activity decreased in response to increased exposure to selenium for several months, but the levels of thyroid hormones in these animals did not show a consistent pattern.

Studies of Chinese populations and laboratory animals exposed to high levels of organic and/or inorganic selenium compounds have not found evidence of selective teratogenic effects in mammals.

There is no evidence to support a causal association between selenium compounds and cancer in humans. In fact, some epidemiological and experimental evidence suggests that selenium exposure under certain conditions may contribute to a reduction in cancer risk. The chemopreventive potential of supplemental selenium is currently under research. Selenium sulfide and ethyl selenac are the only selenium compounds that have been

shown to be carcinogenic upon oral administration in rodents; however, significant exposure of humans to these chemical forms of selenium is extremely unlikely. Additional information on main health effects of selenium in humans and animals is summarized below and detailed in Chapter 3.

Selenosis. Following chronic oral exposure to excessive amounts of the organic selenium compounds in food, the two principal clinical conditions observed in humans are dermal and neurological effects, as described most completely in the epidemiological study of endemic selenosis in the People's Republic of China. The dermal manifestations of selenosis include loss of hair, deformation and loss of nails, and discoloration and excessive decay of teeth, while neurological effects include numbness, paralysis, and occasional hemiplegia. The average dietary intake of selenium associated with selenosis in these people has been estimated to be 1,270 µg/day (~0.02 mg/kg/day, or 10–20 times higher than normal daily intake).

Loss of hair and malformation of hooves in pigs, horses, and cattle, and poliomyelomalacia in pigs have been reported to occur following long-term exposure to excessive amounts (more than 30 times the normal dietary amount of selenium) of the organic selenium compounds found in seleniferous plants. Histologically, swine with selenium-induced neurological signs exhibit bilateral macroscopic lesions of the ventral horn of the spinal cord. The selenium in the selenium-accumulating plant *Astragalus bisulcatus* appears to be a more potent neurotoxicant than D,L-selenomethionine or selenate. The form of selenium in *A. bisulcatus* is unknown, although it is apparently nonprotein. Myocardial degeneration has been experimentally produced in cattle, sheep, and swine (as well as in laboratory mammals) by acute and longer-term exposures to inorganic salts of selenium, but it is unclear whether seleniferous grains or forages, or other natural sources of selenium, cause the same cardiomyopathy.

The neurological signs and histopathology observed in livestock following oral exposure to excess selenium compounds have not been recorded in laboratory animals. This suggests that (1) small laboratory mammals might not be appropriate models for selenium toxicity in humans due to toxicokinetic differences (e.g., laboratory animals absorb selenium compounds to a lesser extent, or metabolize and/or excrete selenium compounds more quickly), (2) some as yet unidentified organic form of selenium contributes to the neurological manifestations of chronic selenosis in humans and in livestock, (3) unrecognized confounding factors, such as other plant toxins, have contributed to the neurological syndrome associated with chronic selenosis in field studies of humans and livestock, and/or (4) species differences in interactions between selenium and other nutrients or xenobiotics, such as vitamin E and methionine, which have been found to be antagonistic to selenium toxicity.

Endocrine Effects. Selenium is a component of all three members of the deiodinase enzyme family, the enzymes responsible for deiodination of the thyroid hormones, and has a physiological role in the control of thyroid hormone levels. Significant decreases in serum T3 hormone levels have been

observed in humans that were environmentally or experimentally exposed to elevated dietary levels of selenium (several times higher than normal). However, the T3 hormone levels observed in these studies were still within the normal human range, so the biological impact of this change is unclear. The effect of increased dietary selenium on other thyroid hormones is also uncertain. Intermediate-duration studies in rats show a decrease in type-I-deiodinase activity in response to elevated selenium; however, the levels of thyroid hormones in these animals did not show any consistent changes.

Reduced growth rate of young animals and weight loss in older animals are two of the most common effects in experimental animals following long-term oral intake of excessive levels of inorganic and organic compounds of selenium. It is quite possible that selenium-induced reduction in growth has a thyroid or other endocrine component. For example, selenite treatment of young rats decreased somatomedin C levels, although somatomedin C was not a sensitive index of elevated selenium exposure in humans from a high-selenium area of South Dakota, and growth hormone secretion in response to the growth hormone releasing factor was also reduced in selenium-treated rats. The primary endocrine target of selenium leading to decreased growth has yet to be elucidated. Pancreatic toxicity has been observed following excess selenium exposure. Cytoplasmic flocculation was observed in lambs treated with a single oral dose of selenite, and pancreatic damage, which was not further described, was noted in rats following chronic oral treatment with selenate or selenite. Pancreatic toxicity associated with excessive selenium exposure is likely related to the unique ability of that organ to accumulate the element.

Reproductive Effects. In humans, no correlation has been found between selenium levels in seminal fluid and sperm count or mobility. No significant increase in spontaneous abortions was reported among women chronically exposed to drinking water containing increased selenium, but the concentration was not considered to be unusually high. In animals, oral exposure to high doses of sodium selenate or selenite (at least 8 times greater than those normally supplied by an adequate diet) caused increased numbers of abnormal sperm, as well as testicular hypertrophy, degeneration, and atrophy in male rats, and affected the estrous cycle in female rats and mice. The animals that showed these effects were not mated, so it is not clear if fertility was affected. Oral treatment with L-selenomethionine similarly caused disturbances in the menstrual cycle (anovulation, short luteal and follicular phases) in monkeys. Selenium deficiency has also been reported to cause decreased sperm production and motility in rats. The relevance of the reproductive effects of high and low levels of selenium in laboratory animals to potential reproductive effects in humans is not known.

Hepatic Effects. Liver effects have not been reported for humans exposed to excessive amounts of selenium. No significant abnormalities were found in blood levels of liver enzymes in people living in high selenium areas, or in liver morphology (ultrasonographic examination) of individuals suffering from severe symptoms of selenosis. In experimental animals and livestock, however, the liver has been shown to be affected following inhalation or oral

exposure to different kinds of selenium compounds. Hepatocellular degeneration occurred in guinea pigs following short-term inhalation exposure to excessive levels (hundreds of times higher than normal) of elemental selenium dust (8 mg/m³) or hydrogen selenide (33 mg/m³). Cirrhosis, hepatocellular degeneration, and changes in liver enzyme levels in serum have been reported for rats, pigs, and mice orally exposed to selenite, selenate, or organic selenium. The oral doses of selenium producing the various adverse liver effects were approximately 10 times the amount normally found in an adequate diet. Excessive dietary exposure to selenium sulfide (several thousands of times higher than normal selenium intake) produced frank hepatotoxicity in rats, but not in mice. Although the liver appears to be the primary target organ for the oral toxicity of selenium in experimental animals following intermediate and chronic exposure, liver cirrhosis or dysfunction has not been a notable component of the clinical manifestations of chronic selenosis in humans. The lack of evidence of liver damage in humans due to selenosis, despite all of the animal data to the contrary, suggests a problem with the animal models of the disease.

Renal Effects. No reports of renal effects in humans were located. In animals, mild kidney effects have been observed following oral exposure to selenium at levels several hundred times higher than normal human intake. These effects include hydropic degeneration in sheep following a single dose of 5 mg Se/kg/day as sodium selenite. Rats appear to be more sensitive than mice to renal effects of repeated oral exposures to selenium compounds. A dose-related increase in renal papilla degeneration, described as mild to minimal, was observed in rats at very high levels of selenate or selenite (0.5 mg Se/kg/day, several hundreds of times higher than normal human intake) in the drinking water for 13 weeks, although increased kidney weight was the only renal effect in similarly exposed mice. Mice that were given excessive daily doses of selenium sulfide by gavage (464 mg Se/kg/day for 13 weeks), however, developed interstitial nephritis.