

Selenium

Function

The trace element selenium is chemically similar to sulfur and may replace sulfur in amino acids (Levander and Burk 1994). The first recognized sign of selenium deficiency, liver necrosis in laboratory animals, was discovered nearly forty years ago. Soon thereafter, combined deficiencies of selenium and vitamin E were shown to cause liver necrosis in rats and swine, exudative diathesis in chickens, and white-muscle disease in sheep and cattle. In humans, selenium deficiency is associated with myopathies such as Keshan Disease, a cardiomyopathy that is endemic in some areas of China. This deficiency results from the low selenium content of the soil in certain provinces and thus in the crops that are grown there. Selenium-deficient soils are not limited to China and have been identified in many other countries, including Finland and New Zealand.

The discovery more than twenty years ago that selenium is a constituent of the antioxidant enzyme glutathione peroxidase provided a biochemical basis that seems to be at least partly responsible for the essentiality of selenium (Levander and Burk 1994). More recently, its role in thyroid gland activity was demonstrated, specifically as part of the active center of the enzyme type I iodothyronine deiodinase, which converts the prohormone thyroxine (T4) to the active hormone triiodothyronine (T3).

Dietary forms of selenium that are nutritionally useful include the inorganic forms selenite and selenate, and the organic forms selenomethionine and selenocysteine. Selenium can be incorporated into growing yeast, which then provides nutritionally useful forms of selenium for animals and humans. Much of the selenium in yeast is selenomethionine, a form that is virtually 100 percent absorbed. Average total dietary selenium intake in the U.S. has been estimated at 100 and 70 μg per day for men and women, respectively (Levander and Burk 1994).

The epidemiological association of higher selenium intakes with reduced cancer risk and the antioxidant role of selenium in glutathione peroxidase (as well as several other possible mechanisms) have provided a basis for research on possible anticarcinogenic effects of selenium. Several selenium compounds have been shown to have anti-tumorigenic activities in a variety of animal models when administered at levels greater than those associated with nutritional need (Combs 1994).

Only two clinical intervention trials published to date were designed to determine whether selenium in combination with other nutrients would reduce cancer risk.

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In one, 50 µg of selenium (in yeast), in combination with vitamin E and beta-carotene, moderately reduced the risk of total mortality, total cancer mortality, and stomach cancer mortality (Blot et al. 1993). In the other, inorganic selenium—together with a wide spectrum of other minerals and vitamins—did not significantly protect against cancer (Li et al. 1993). An additional placebo-controlled, randomized clinical trial was stopped for ethical reasons after it became clear that treatment with 200 µg of selenium in yeast had significantly decreased lung cancer and overall cancer mortality, as well as incidence of colorectal and prostate cancer (Clark et al. 1996; Combs and Clark 1997). The primary objective of the trial was to determine the effect of selenium on non-melanoma skin cancer, on which there was no effect, either negative or positive.

Safety Evidence

Excess selenium intake from consumption of seleniferous plants by animals produces a wide range of adverse effects (National Research Council 1983). Chronic toxicity signs in livestock include cirrhosis, lameness, hoof malformations, hair loss, and emaciation. In laboratory animals, the signs most commonly include cirrhosis. The dietary level of selenium recognized to produce adverse effects in farm animals is 4 to 5 µg or more per g of dry weight of diet.

One episode of human poisoning by selenium involved a manufacturing error that resulted in a dietary supplement product containing 182 times the amount of selenium declared on the label (Jensen et al. 1984; Helzlsouer et al. 1985). Adverse effects occurred within a few weeks and included changes in the hair, nails, and liver. Human selenium poisoning in a high-selenium area of China also produced adverse effects on the nails, skin, nervous system, and teeth (Yang et al. 1983). These occurred in susceptible persons with intakes of 910 µg per day or more. No such results have been associated with lower levels of intake, but the ratio of plasma selenium to erythrocyte selenium has been found to increase with dietary intakes of 750 µg per day or more (Yang et al. 1989b). Human surveys in seleniferous areas of the U.S. have failed to find any signs of selenium intoxication with intakes of up to slightly more than 700 µg per day (Longnecker et al. 1991). Because the chemical forms of selenium in foods grown in seleniferous areas are not known, the human data on adverse effects from chronically high intakes apply only to total dietary selenium and not to any specific form. No adverse effects were observed in the eight- to ten-year clinical trial by Clark and coworkers (Clark et al. 1996; Combs and Clark, 1997) at daily supplemental intakes of 200 µg of selenium in yeast. Most of the selenium in this yeast preparation was in the form of selenomethionine.

Ultimately, the adverse effects established in a few individuals at chronic dietary intakes of 910 µg per day qualify that value to be identified as the selenium LOAEL. Another study (Yang et al. 1989b) did not find any overt adverse effects,

but did find an increase in the ratio of plasma selenium to erythrocyte selenium at intakes of 750 µg per day. Although this change in ratio is not in itself an adverse effect, it may indicate that the ability to eliminate excess selenium is nearly saturated. Application of regression methods to these data (Yang et al. 1989a, 1989b) supports a NOAEL for total dietary selenium of 853 µg per day in the Chinese adult of 55 kg weight (Poirier 1994; Combs 1994).

Published Official Reviews of Selenium Safety

The FNB judged the reexamination of selenium intakes by Yang and Zhou (1994) to identify a selenium NOAEL of 800 µg per day (Food and Nutrition Board 2000). A UF of 2 was selected to provide protection for sensitive individuals, and thus FNB derived a UL of 400 µg selenium per day for adults for total oral intake from all sources. The FNB has not expressed an opinion on safe levels for selenium supplementation, except that implied by a total intake UL of 400 µg.

The EC SCF considered the data of Yang and coworkers (Yang et al. 1989b) sufficient to identify a NOAEL of 850 µg per day (Scientific Committee on Food 2000). A UL of 300 µg was derived from this NOAEL by application of a UF of 3 and rounding the result. The EC SCF noted that this 300 µg UL was supported by the absence of adverse effects in a clinical trial by Clark and coworkers involving a supplement of 200 µg and diets of approximately 100 µg (Clark et al. 1996).

The UK EVM did not identify a NOAEL but considered the Chinese studies (Yang et al. 1989a, 1989b) to support a LOAEL of 910 µg per day (Expert Group on Vitamins and Minerals 2003). The UK EVM applied a UF of 2 to this LOAEL for a large population with a lifetime of exposure and derived a total selenium SUL of 450 µg, and a supplemental selenium SUL of 350 µg.

The EPA has set its NOAEL at 0.015 mg per kg per day (Poirier 1994). In a Chinese population with an average LOAEL of 910 µg, the lower 95 percent confidence limit was 600 µg per day (Yang and Zhou 1994). The EPA selected a UF of 3 to calculate an RfD equivalent to 350 µg for a 70 kg adult (Environmental Protection Agency 2004).

CRN ULS for Selenium

The exact forms of selenium consumed by the Chinese population in the epidemiological studies are not known, but it seems likely that much of it would have consisted of selenomethionine, as in the clinical trial by Clark and coworkers. Considering the variability of dietary intakes, a supplemental selenium NOAEL of 200 µg is identified from the clinical trial data. Based on the absence

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of adverse effects at this supplemental level, and on the substantial margin of safety it provides below levels associated with adverse effects, a UF of 1.0 is appropriate, and the CRN ULS for selenium is determined to be 200 µg per day.

When dietary selenium is 100 µg per day, the CRN ULS identified by this direct method for selenium supplementation safety would result in a total intake of 300 µg—equivalent to the EC SCF UL and the UK EVM values.

Comparison of Safety Values for Selenium

CRN ULS	200 µg
US FNB UL	400 µg
EC SCF UL	300 µg
EC supplement maximum	Not established (as of May 2004)
UK EVM SUL	350 µg supplement; 450 µg total

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