Selenium

Introduction

Selenium is a trace element that is chemically similar to sulfur and replaces sulfur in the cysteine in certain enzymes (Levander and Burk 1994). Although toxic in large amounts, selenium is a necessary element for humans and some populations suffer from low selenium. The first recognized sign of selenium deficiency, liver necrosis in laboratory animals, was discovered more than 40 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 a few 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 several other countries, including Finland and New Zealand.

The discovery 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 (Centers for Disease Control [CDC] 2012). 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 after oral ingestion; selenomethionine is readily converted to selenocysteine—the form incorporated into certain enzymes. Average total dietary selenium intakes in the U.S. have been estimated at 100 and 70 µg per day for men and women, respectively (CDC 2012).

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 antitumorigenic activities in a variety of animal models when administered at levels greater than those associated with nutritional need (Rayman 2012).

Two clinical intervention trials published in the mid-1990s were designed to determine whether selenium in combination with other nutrients would reduce cancer risk. In one, 50 µg 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 the incidence of colorectal and prostate cancer (Clark et al. 1996a, 1996b; Combs and Clark 1997). The amount of selenium used in the study (200 µg) was nearly 3 times the adult male RDA (70 µg) (Institute of Medicine [IOM] 2000). The primary objective of the trial was to determine the effect of selenium on nonmelanoma skin cancer, but there was no effect, either negative or positive, on that disease.

Safety Considerations

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 higher per gram dry weight of diet.

One episode of human poisoning by selenium involved a manufacturing error that resulted in a dietary supplement product containing approximately 200 times the amount of selenium declared

on the label (MacFarquhar et al. 2010; Aldosary et al. 2012). 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, Yin, et al. 1989). Human surveys in seleniferous areas of the U.S. have failed to find any signs of selenium intoxication with intakes up to slightly more than 700 µg per day (Longnecker et al. 1991). Because not all the chemical forms of selenium in foods grown in seleniferous areas are 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 8- to 10-year clinical trial by Clark and coworkers (Clark et al. 1996a, 1996b; Combs and Clark 1997) at daily supplemental intakes of 200 µg 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 for identification as the selenium LOAEL. The data of Yang, Yin, et al. (1989) 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 the data of Yang, Zhou, et al. (1989) and Yang, Yin, et al. (1989) supports a NOAEL for total dietary selenium of 853 µg per day in the Chinese adult of 55 kg weight (Combs 1994; Poirier 1994).

Cancer

A number of observational studies suggested that death rates from cancer, including lung, colorectal, and prostate cancer, are lower among people with higher blood levels or intakes of selenium (Patterson and Levander 1997; Russo et al. 1997; Young and Lee 1999). Some clinical trials have indicated that increased selenium intakes may lead to lower risks of a number of types of cancer (Clark et al. 1996a, 1996b), and epidemiological data (actually a nested case control

study as a later analysis of data from a large clinical trial—the Health Professionals Follow Up Study) suggested that selenium was associated with a lower incidence of type II diabetes (reviewed and summarized by Rajpathak et al. 2005). To more thoroughly test these possible relationships, two large clinical trials—the SELECT trial (Lippman et al. 2009) and the SU.VI.MAX study (Hechberg et al. 2004)—were conducted. Both trials monitored type II diabetes as well as a number of types of cancer.

The design of the SELECT trial was driven primarily by the results of lower rates of several cancers but not the one most expected—skin cancer—in the selenium trial of Clark et al. (1996a, 1996b) and by the vitamin E results (lower rates of prostate cancer) in the ATBC study (Heinonen et al. 1998). Although the Clark study had provided 200 µg selenium as selenized yeast (yeast grown in a high-selenium medium), the SELECT trial provided selenium (in the same amount) as selenomethionine. The 200 µg dose is well above the IOM's RDA (55 µg) and well below its UL (400 µg).

The ATBC study found a 32 percent decrease in clinically evident prostate cancer among those taking alpha-tocopherol (50 IU), compared with the placebo group; mortality from prostate cancer was 41 percent lower in those taking vitamin E. The SELECT trial did not find any protection against prostate cancer by either selenium or vitamin E (Lippman et al. 2009).

The SU.VI.MAX study examined the effects of a complex supplement containing moderate amounts of vitamin E and C, beta-carotene, zinc, and selenium versus placebo on the risk of chronic diseases such as cancer, cardiovascular disease, and diabetes. Men who began the study with normal (<3 ng per ml) prostate specific antigen (PSA) levels had their prostate cancer risk reduced by half (Meyer et al. 2005). In men whose PSA levels were elevated (>3 ng per ml) at the beginning of the study, however, use of the supplement was associated with a nonsignificant small increase in prostate cancer risk. Overall, the SU.VI.MAX data indicate that the supplement was highly protective for men with low PSA levels and that it either had no impact or possibly caused a small increase in risk for those with high PSA levels.

More recently, the SELECT trial data (Lippman et al. 2009) indicate no significant overall effect on prostate cancer risk for selenium given to men, many of whom may have had elevated PSA levels (African American men ages 50 and older and white men ages 55 and older).

In summary, the SELECT and SU.VI.MAX results together indicate that a selenium-containing supplement is protective for men with low PSA levels, but is either non-effective or may carry a very small risk for those with higher PSA levels. In addition, data on selenium concentrations in toenail clippings suggest that increased selenium intake over a narrow but relatively low intake range is highly protective against prostate cancer risk (Hurst et al. 2012).

Type II Diabetes

Evidence is mixed and seemingly contradictory on the effect of selenium intake on type II diabetes. Rajpathak et al. (2005) reported that levels of toenail selenium are lower among diabetic men with or without cardiovascular disease than among healthy controls. The odds ratio (similar to relative risk) was 0.45 for the highest compared with the lowest quartile of toenail selenium concentration.

More recently, Bleys et al. (2007a) examined data from the Third National Health and Nutrition Examination Survey (a large, multiyear observational, or epidemiological, study) and found that adults with diabetes had very slightly higher serum selenium concentrations compared with nondiabetics. Before the data were adjusted for a number of factors (gender, age, ethnicity, etc.), the differences were very small and nonsignificant. After adjustment, the mean serum selenium concentrations of selenium were as follows: diabetics 126.8 ng per ml, and nondiabetics 124.7 ng per ml. Because of the large number of persons evaluated, this small difference was labeled as "significant" ($P = 0.02$). A follow-up publication (Bleys et al. 2007b) declared in the article title that these data are "more bad news for supplements."

Several factors fail to support or even contradict the validity of the Bleys et al. observations and conclusions. First is the lack of biological plausibility; it is unlikely that such small differences in selenium concentrations would have a causal relationship to diabetes. Second, there is no

evidence of a dose-response relationship. Only one clinical trial (Stranges et al. 2007) seems to support Bleys and coworkers. Moreover, newer observational studies continue to support a substantial effect of higher selenium intakes as being protective against type II diabetes (Park et al. 2012).

Official Reviews

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

European Commission's Scientific Committee on Food (EC SCF 2000). The EC SCF considered the data of Yang, Yin, and coworkers (1989) sufficient to identify a NOAEL of 850 μg per day. A UL of 300 μg was derived from this NOAEL by application of a UF of 3. 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 (1996a, 1996b). The EC has not set a regulatory maximum for selenium added to supplements as of the writing of this book.

Expert Group on Vitamins and Minerals (EVM 2003). The UK's EVM did not identify a NOAEL but considered the studies of Yang and coworkers (Yang, Yin, et al. 1989; Yang, Zhou, et al. 1989) to support a LOAEL of 910 μg per day. Furthermore, the EVM, applying a UF of 2 to a LOAEL for a large population with a lifetime of exposure, derived an SUL for selenium of 450 μg.

The EVM noted that its SUL is consistent with the clinical trial data by Clark and coworkers. These expert groups have not offered any explanations for why their NOAEL, LOAEL, and uncertainty values are so different.

CRN Recommendations

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 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 sufficient, and the CRN UL for selenium supplements 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 SCF UL. Somewhat larger amounts should be safe but the margin of safety would be less generous.

Quantitative Summary for Selenium

CRN UL, supplemental intake	200 μg/day
IOM UL, total intake	400 μg/day
EC SCF UL, total intake	300 μg/day
EC supplement maximum	Not determined
EVM SUL	350 μg/day supplemental intake; 450 μg/day total intake

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