

The Nutritional Relationships of Selenium

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Selenium was discovered by Berzelius in 1817. Eventually its electrical and optical properties were recognized, which stimulated a great deal of research and development in the electrophotographic field. This led to the use of selenium in the xerographic, or photocopier processes.

Initially there was little biological interest in the mineral selenium except for its toxic properties. Selenium toxicity was first recognized and described in animals. Cattle grazing on certain plants grown in seleniferous soil developed a peculiar condition called alkali disease, or blind staggers, which would eventually lead to death. It was believed that humans living in the same regions could also be affected by too much selenium, however, toxicity in humans was not readily recognized.¹

Interest in selenium increased due to the discovery of a selenium compound called "factor 3." This compound was found to protect animals from fatty infiltration and necrosis of the liver. This also led to the speculation that some type of relationship existed between selenium and vitamin E.² Research by Schwarz and Foltz, at the National Institutes of Health in 1957, found that selenium deficiency produced recognizable abnormalities in lab animals. They found that selenium supplementation reversed a condition called white muscle disease that occurred in sheep and cattle raised on selenium deficient soils. This led to the suspicion that selenium may be involved as a cofactor in enzyme systems related to cellular oxidation, and that selenium may therefore, play a role in human nutrition as well. The discovery that selenium deficiency was related to disease conditions brought selenium to the forefront as one of the latest essential nutrients.

The research of Rotruck and colleagues found that a deficiency of selenium resulted in oxidative damage to red blood cells, which was related to reduced activity of an enzyme, glutathione peroxidase. This enzyme reduced the effects of hydrogen peroxide upon

hemoglobin. Eventually it was found that selenium was a component of the glutathione peroxidase enzyme, thereby, establishing a direct biochemical role for selenium.³

Selenium Toxicity and Deficiency In Animals

The effect of selenium toxicity and deficiency have been well described in animals, and vary according to species.⁴ Selenosis occurs mostly in ruminants, or grazing animals due to the consumption of selenium accumulating plants, such as locoweed. These plants preferentially accumulate selenium when the mineral is present in the soil in high concentrations. The accumulator plants can convert inorganic selenium into a utilizable form. However, after these plants die the organic form of selenium is returned to the soil and can then be utilized by other plants as well. Areas of high selenium soils are found in the North American plains, Wyoming, South Dakota, Nebraska, and Oregon. Other countries known to have high selenium areas include, Australia, Israel, Ireland, South Africa, South America, the former Soviet Union, France, Germany, and China. Symptoms of toxicity that have been described include:

Acute Selenium Toxicity

Symptoms in Animals

Abdominal pains	Blindness
Excessive salivation	Partial paralysis
Respiratory distress	Starvation

Chronic Selenium Toxicity

Symptoms in Animals

Rough coats	Hair loss
Lameness	Pain and sloughing of hooves
Erosion of joints	
Liver cirrhosis	Cardiac Atrophy
Lowered conception rates	Anemia (in all species)
	Birth defects

The mechanism of selenium toxicity remains uncertain. However, it may be due to the effects of excess selenium inhibiting dehydrogenase enzymes, and removal of sulfhydryl groups essential to cellular

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oxidative processes. Antagonism of other nutrients, as well as deficiencies, and excesses may also play a significant role in selenium toxicity.

Selenium is necessary for reproduction and growth in animals and is known to protect against a number of diseases. Conditions such as white muscle disease, exudative diathesis, pancreatic fibrosis, and liver disease are prevented by adequate selenium in various species. These conditions have been related to excessive free radical formation, and reduced glutathione peroxidase activity.

Selenium In Human Nutrition-Deficiency

The most recognized condition associated with selenium deficiency in humans is Keshan disease, which is a cardiomyopathy affecting mostly children, and young women.^{5,6} This condition was discovered in individuals living in areas of China, where low selenium soils exist. Grains and cereals that were consumed as the major staples in the diet contained little, if any selenium. Supplementation of selenium produced a positive response in individuals suffering with Keshan disease.

Kashin-Beck disease is also found in individuals living in low selenium areas. Kashin-Beck is an osteoarthritic condition affecting children in the developmental years. It is also known as "big-joint" disease due to swelling, and calcium deposition in affected joints. It is believed that selenium deficiency alone is not the sole cause of these conditions, however. Prasad has reviewed a number of conditions that may be related to selenium deficiency.⁷ These are summarized below.

Cataracts

Selenium concentrations normally increase in the human lens from birth to old age. The selenium content of lenses with cataracts was found to be markedly reduced, less than one sixth, compared to normal lenses in the same age group. Glutathione is also present in high amounts in normal lenses compared to those with cataracts. Some drugs, due to their production of excessive peroxides during their metabolism are known to cause cataracts. Any factor that antagonizes selenium, or the selenium-dependent glutathione peroxidase system, can allow oxidative damage to occur. Therefore, selenium deficiency, as well as xenobiotics, drugs, and heavy metals such as

mercury, can contribute to cataract formation.

Erythrocyte Disorders

Hemolytic anemia, as well as simple iron deficiency anemia, has been associated with reduced glutathione peroxidase activity. Reduced glutathione peroxidase has been reported in normal and premature infants, and with neonatal jaundice. Glanzmann's disease, a platelet disorder that results in excessive bleeding, is associated with reduced glutathione peroxidase activity.

Schrauzer, also reviewed studies associated with selenium deficiency,⁸ and are discussed below.

Aging

During normal metabolism, each cell is subject to approximately one thousands "oxidative hits" per day. This is normal and is thought to contribute to the normal aging process. However, excessive free radical production, or a reduced ability to quench the normal production of radicals is thought to contribute to premature, or accelerated aging. Selenium deficiency has been associated with degenerative conditions of aging, due to decreased glutathione peroxidase activity. These include premature aging, lipofuscin deposition, and chronic inflammatory conditions.

Cancer

Experimental studies have demonstrated a protective effect of selenium on mammary tumor formation, and reduced tumor growth rates in animals. Selenium deficiency, in conjunction with low vitamin E, has been related to a greater incidence of lung, skin, and gastrointestinal cancers in humans. Selenium protects against chromosomal damage, stimulates DNA repair, and modulates the rate of cell division. Selenium also has an inhibitory effect upon chemical carcinogens and accelerates their detoxification.

Immune Competence

Selenium, in conjunction with vitamin E, enhances antibody formation.⁹ Therefore, selenium deficiency may impair the normal immune response. Studies have revealed low selenium status in AIDS patients, and has been associated with progression of the disease.^{10,11} There are similarities between AIDS

cardiomyopathy, and cardiomyopathy found in Keshan disease, and reports have indicated improvements in AIDS related cardiomyopathy as result of selenium therapy.

Sudden Infant Death Syndrome (SIDS)

A commentary by Oldfield, sighted studies associating selenium deficiency with (SIDS).¹² This remains controversial at this time however.

Cystic Fibrosis

Oldfield, also sighted studies speculating the relationship between selenium deficiency and cystic fibrosis. Wallach, has shown convincing evidence of this relationship. He reported a direct relationship of cystic fibrosis in the rhesus monkey with selenium, and zinc deficiency. Wallach, relates a strong indirect relationship to cystic fibrosis in humans and selenium deficiency, in conjunction with deficiencies of vitamin E, and zinc. Liver analysis of selenium in children with cystic fibrosis showed a significant reduction of selenium compared to normals.¹³

Crohn's Disease

A study of patients with Crohn's disease found that a reduction of selenium, and glutathione peroxidase in plasma and erythrocytes existed in forty percent of an affected group. They also found that patients with bowel resections of two hundred centimeters or more, were at a high risk for developing selenium deficiency due to malabsorption.^{14,15}

Thyroid

Selenium has been shown to be related to thyroid function. The enzyme l iodothyronine deiodinase (IDI) is a selenoenzyme, which is responsible for the peripheral conversion of T4 to T3 in the liver, and kidneys. IDI activity is reduced in the presence of selenium deficiency.¹⁶

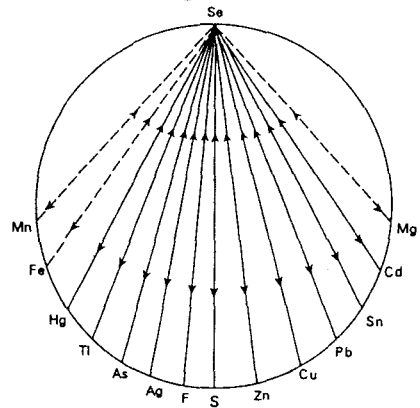
Factors Contributing to Selenium Deficiency

There are several factors that can contribute to selenium deficiency other than reduced intake. Figure 1, shows the minerals that are antagonistic to selenium. The solid lines represent the known antagonism, and the broken lines indicate suspected antagonism.

Sulfur (S) protects from selenium toxicity.

However, large amount of selenium can interfere with normal sulfur metabolism.¹⁷

Figure 1.
Minerals Antagonistic to Selenium



The antagonistic effects between selenium and silver (Ag), arsenic (As), cadmium (Cd), mercury (Hg), and Thallium (Tl) has been described by Ganther.¹⁸ It should be noted that selenium does protect tissues from the toxic effects of heavy metals, but excretion of toxic heavy metals are not increased by selenium therapy. Selenium apparently binds these metals, such as mercury and cadmium, rendering them less damaging to cells and tissues.

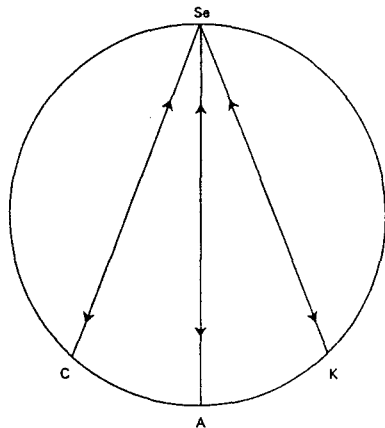
Fluorine (F) has been shown to counteract the effects of selenosis.¹⁹ This has been found in areas with high levels of both selenium, and fluorine. Selenium was not toxic even with a high body burden when fluorine was also present.

Antagonism of lead (Pb), tin (Sn), and zinc (Zn) has been sited by Schrauzer.²⁰ More recent investigations have confirmed the zinc-selenium antagonism.²¹ Copper (Cu) has also been shown to be a selenium antagonist.²²

On the basis of TMA studies it is suspected that selenium is antagonistic to magnesium. This is due to the potential sodium raising effect of selenium. Sodium increases the excretion of magnesium. Magnesium is also essential for the synthesis of glutathione,²³ and a deficiency can increase the effects of selenium toxicity.²⁴

The possibility of iron, and manganese antagonism by selenium also exists. Anemia is a consistent finding in animals, and humans with selenium toxicity. Figure 2, illustrates the

Figure 2.
Vitamins Antagonistic to Selenium



vitamins that are considered antagonistic to selenium. Animals suffering from selenosis were found to have decreased levels of vitamin A, and ascorbic acid.²⁵ Ip, reported that the protective effect of selenium on mammary carcinoma in animals was nullified by high vitamin C supplementation.²⁶ Selenium toxicity in laboratory animals is associated with a corresponding decrease in the levels of vitamin C, and vitamin K.²⁷

The nutrients shown in figure 1 and 2, can be antagonized by excessive selenium accumulation. They in turn can inhibit the toxic effects of selenosis.

Nutrients Synergistic to Selenium

Vitamin E is well recognized as a selenium synergist. Vitamin E is a fat soluble antioxidant that protects the lipid cell membranes from the effects of oxidation. Vitamin E supplementation can reduce the symptoms of selenium deficiency.

Cobalt (Co) has also been shown to be synergistic to selenium. A diet containing high amounts of selenium did not produce selenium toxicity symptoms in lab animals initially. However, when cobalt was added in equal amounts, symptoms of selenosis developed.²⁸

Vitamin B₆ acts as a selenium synergist, and is associated with the conversion of selenomethionine to glutathione peroxidase.²⁹

Even though in some circumstances, vitamin C can antagonize selenium, in others it can enhance selenium utilization. Human studies have revealed that vitamin C plays a role in the

maintenance of selenium homeostasis.^{30,31}

Copper has also been shown to be synergistic to selenium. Animal studies have revealed that glutathione peroxidase activity decreased during copper deficiency.^{32,33}

Human Selenium Toxicity

Selenium has been recognized as a toxin for many years before it was determined to be a required nutrient. Toxicity symptoms have been extensively studied, and reported in high selenium areas of China,³⁴ and has since been reported in the United States, and other countries.

Sources of Selenium

Industry has been responsible for selenium intoxication for decades. Fishbein, categorized the primary and secondary industrial exposures to selenium.³⁵ Primary industries include mining, ore extraction, including copper, zinc, lead, pyrite roasting, and the production of lime, and cement. These industries expose workers to various types of selenium containing dusts. Secondary sources produce organic vapors and fumes containing selenium compounds that include the manufacture of glass and ceramics, steel and brass production. Vulcanizing, and curing of rubber products release organic selenium vapors. Selenium is a potential hazard in the plastic and electronic industry, and is contained in paint pigments, and printing inks. Chiau, and colleague cited reports of high selenium concentrations in paper products, which when burned, give off a significant amount of selenium. These levels are high enough to be considered toxic.³⁶

Selenium intoxication has been found in individuals taking nutritional supplements. The supplements contained much more selenium than the amounts listed on the labels. The average selenium intake of individuals affected by selenium toxicity in seleniferous areas of China was approximately 5 milligrams per day.³⁷

Symptoms of Selenium Toxicity

The signs and symptoms of selenium toxicity have been described by several investigators, and even though the sources vary, the symptoms are very similar. Symptoms of industrial exposure have been described by Fishbein, depending upon the type of selenium

the workers were exposed to. Acute exposure produced irritation of the eyes, nose, and throat, burning sensation of the nostrils, sneezing, coughing, congestion, and dizziness. Dyspnea, headaches, and edema of the uvula were found with heavy exposures. Chronic exposure has produced hypochromic anemia, leukopenia, irregular menses, and a garlic breath odor, or metallic taste.

Symptoms associated with excessive ingestion of selenium from supplements described by Levander and Burk, include nausea, vomiting, hair loss, changes in the nails, fatigue, irritability, and peripheral neuropathy.

Changes occurring in individuals living in high selenium soil areas include, nausea, vomiting, skin depigmentation, hair loss, and low hemoglobin.³⁸ Dental caries has been a consistent finding in regions of selenosis. The effect of selenium on the teeth has been confirmed by animal studies.³⁹

A case of selenium toxicity was reported with the use of a selenium-containing anti-dandruff shampoo when skin lesions were present. The selenium was readily absorbed through the open skin. Symptoms included tremors, and appetite loss, which improved with discontinuation of the product.⁴⁰

Interestingly, the topical application of selenomethionine has proven beneficial in protecting against skin cancer caused by ultraviolet irradiation.⁴¹

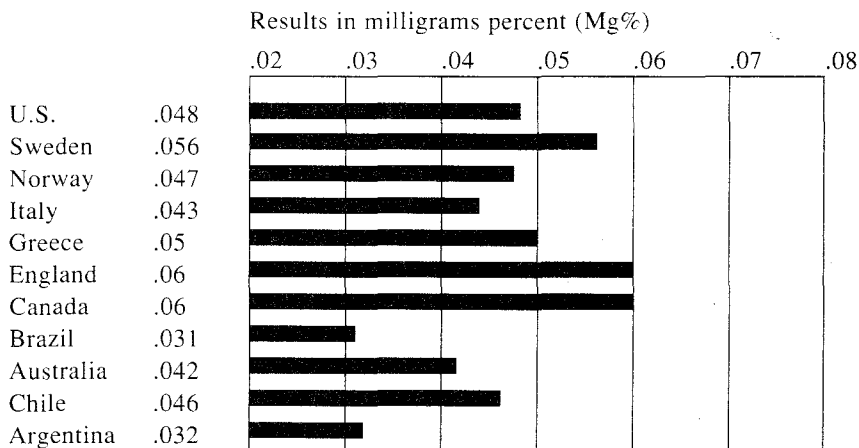
Sources of Selenium and Body Distribution

The selenium content of cereals and grains are considered good sources of the mineral. However, the content would vary depending upon the amount of selenium present in the soil, as well as preparation methods. Seafood, kidney, liver, meats, and poultry are good sources. Fruits and vegetables, except for garlic and asparagus are poor sources of selenium.

Selenium is distributed throughout the body with the highest concentrations found in the kidneys and liver. Whole body selenium content has been estimated at 3 - 6 milligrams in individuals living in low selenium areas, and approximately 13 milligrams in other regions.⁴²

A U.S. recommended daily allowance for selenium has not been established, however, a safe and adequate daily intake has been estimated to be 50 to 200 micrograms for adults and children above the age of 7.⁴³ This range has been extrapolated from animal studies. It is estimated that Americans, and Canadians, consume between 62 and 216 micrograms in their daily diet.⁴⁴ Canadians, apparently have a higher intake than Americans. This is apparent from the hair tissue mineral analysis (TMA) studies conducted by this laboratory on individuals living in different countries, and is depicted in Table 1.

Table 1. Hair Selenium Levels of Individuals From Various Countries



Note: These values are averages, based upon multiple samples from each country. Tests were performed by the procedures established by Trace Elements, Inc.

Assessment of Selenium Status

The mean concentration of selenium in whole blood was found to be 20.6 ug/100ml in a U.S. population. The range was 10-34 ug/100ml. Similar findings were reported in a Canadian population. The findings did range somewhat to the local distribution of selenium.⁴⁵

Selenium status has been reported in pathological conditions. Children suffering from kwashiorkor had a mean level of 11 ug/100ml compared to 23 in control groups. A reduction has been noted in burn patients. Interestingly, red cell selenium was normal in the deficient groups. Plasma, or serum levels are apparently better for determining selenium status than whole blood. Serum levels have been reported at 9.8 ug/100ml.⁴⁶ Other conditions associated with low selenium include, alcoholic cirrhosis, cancers, muscular complaints, hypertension, atherosclerosis, arthritis, muscular dystrophy, infertility, macular degeneration, and diabetic neuropathy.⁴⁷

The use of plasma, or erythrocyte glutathione peroxidase has been found useful in evaluating selenium deficiency.⁴⁸ However, analysis of this selenium-dependent enzyme, although excellent for determining a deficiency, is not sufficient for monitoring adequate, or toxic levels.

Tissue mineral analysis (TMA) of the hair has been used in the study of Keshan disease, and researchers have shown that the blood and hair selenium levels are closely related.⁴⁷ TMA, is very useful in evaluating selenium in relationship to the other antagonistic, and synergistic mineral co-factors.⁴⁹

Conclusion

Even though selenium has gained a great deal of interest in the nutritional field, there is still a great deal to be learned about this important trace element. The focus of selenium research has been on its' involvement in the anti-oxidant system. However, its' biological involvement may be far more extensive. As with any nutrient, selenium should not be viewed in isolation. A deficiency, or excess of selenium will have an impact on several other nutrients. Therefore, assessment of an individual's selenium status should be made in conjunction with the antagonists, synergists, and other co-factors.

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Reprinted from **The Journal of Orthomolecular Medicine**

First Quarter 1994 – Volume 9 Number 2

Publication Office: 16 Florence Ave., Toronto, ON, Canada M2N 1E9

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