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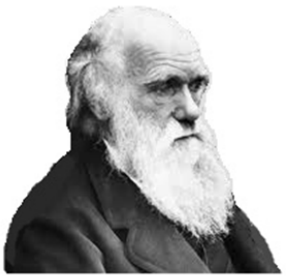

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Toxicological Significance of the Occurrence of Selenium in Foods

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ABSTRACT

The presence of selenium (Se) in foods and the pertinent toxicological data are reviewed. In most regions of the world, the average daily intake of man is thought to be between 60 and 250 micrograms for adults and between 4 and 35 micrograms for infants. The current practice of adding selenium supplements to animal feeds may increase the selenium content of meats by up to 30%, but this does not result in a biologically meaningful increase in the selenium intake of people. Se is mostly absorbed after ingestion, according to the available metabolic data. Up to 50% of it is eliminated in the urine, while the remaining percentage builds up primarily in the liver and kidneys. Recent epidemiological and animal studies show that Se is not a carcinogen, and in some cases may have anti-cancer properties. Neither the essentiality for man, nor the no-effect level of Se have been established.

Keywords: Selenium, Toxicological, Anti-cancer, Diet

1. INTRODUCTION

Selenium was discovered in 1817 in Gripsholm, a Swedish city, by a Swedish chemist Jacob Berzelius [1], who was working in a chemical factory producing, among others, sulfuric acid and nitric acid. One of the raw materials that had been used in the production process was pyrite (iron sulphide), which was obtained from a mine in Falun. It was observed that, when

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ores from Falun were used in lead chambers of installations, reddish sediment was obtained. Initially, it was thought that arsenic compound was responsible for that characteristic sediment; hence, because of fear of its harmful effects, pyrite ores from Falun were avoided from being processed. The phenomenon was, however, regarded as curious and worth further assessment

The results of sample analysis indicated a likely presence of tellurium; however, Berzelius questioned this result. At the beginning of 1818, Berzelius repeated the experiments in a laboratory in Stockholm and found that the sediment investigated contains a new, previously undiscovered element, with properties similar to sulphur [2]. This substance was called selenium, from the Greek word “selene”, which means moon [3].

Increased interest in the biological role of selenium was observed in the 1950s, when it was discovered that this element exerts toxic effects. Increased accumulation of this element led to dystrophy of cardiac muscle or acute hepatic necrosis. [4]. In 1973, the biochemical role of this element was explored, and it was found that selenium belongs to a part of the active center of glutathione peroxidase. After 17 years, it was observed that other enzymes also include this element in their active centers, for example, selenocysteine is a part of the active center of the iodothyronine deiodinase. Studies conducted on the identification of selenoenzymes and selenoproteins initiated intensive studies on the role of this element in human and animal organisms [5].

1. 1. Selenium

Selenium is an essential trace mineral found in soil, water, and some foods. It is an important factor in many body processes. Selenium is a trace element that is naturally present in many foods, added to others, and available as a dietary supplement. Selenium, which is nutritionally essential for humans, is a constituent of more than two dozen selenoproteins that play critical roles in reproduction, thyroid hormone metabolism, DNA synthesis, and protection from oxidative damage and infection.

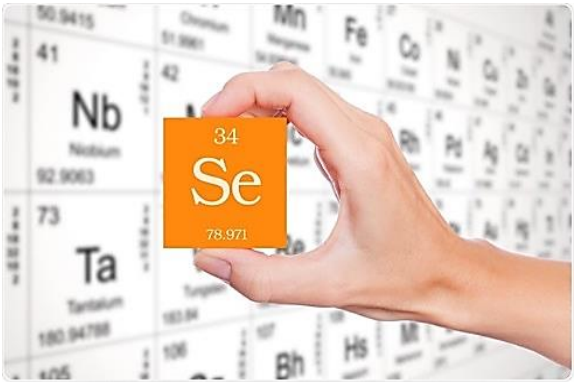

Figure 1: Selenium.

1. 2. Physicochemical properties of selenium

Selenium is found in group 16 of the periodic table, which also includes oxygen, sulfur, polonium, tellurium, and livermorium. This group is called oxoacids. Chemical properties of the elements in this group vary significantly with the increase in the atomic mass of the

elements. Oxygen and Sulfur are typical non-metallic elements, selenium and tellurium are semimetals exhibiting properties of transition semimetals, and polonium has metallic characteristics. Selenium in the environment is found in elemental state (Se^0), in the form of selenides (Se^{2-}), selenates (SeO_4^{2-}), or selenites (SeO_3^{2-}) [6]. This element is characterized by an ease of transition to adjacent oxidation states. These transformations are influenced by several factors such as pH, concentration of free oxygen, redox potential, and humidity. Anaerobic conditions and acidic environment favor the formation of selenium compounds in lower oxidation states. Under aerobic conditions and at alkaline pH, higher oxidation states of this element are dominant [7].

Table 1. Selected Physical and Chemical Properties of Selenium

PROPERTIES	SELENIUM
Electronic configuration	$[Ar]3d^{10}4s^24p^4$
Atomic Number	34
Atomic Weight	78, 96
Density [g/cm^3]	4,808
Melting temperature (ºC)	220
Boiling temperature (ºC)	685
Oxidation states	-11, 0, iv, vi
Electron affinity	-4, 2, Ev
Ionization potential	9.75Ev

Selenium in a free state can be found in five allotropic forms, two of which are amorphous, and the remaining three are crystalline. It can form molecules of ring structure, consisting of eight atoms and chain molecules that are characterized by a considerable length. Ring-shaped molecules Se8 are unstable and possess crystalline forms α and β characterized by a red color.

These are formed as a result of transformation of red elemental selenium, which is obtained by the condensation of selenium vapor. Chain molecules are present in the molten selenium of high viscosity. Sudden cooling of such alloy leads to the formation of gray amorphous selenium also known as vitreous selenium. Chain particles can also be found in gray selenium, also known as metallic selenium, which is the most stable variant of this element. This variant is obtained by heating other selenium varieties to a temperature of 470 K. It is characterized by a very low electrical conductivity in the dark, which increases significantly as a result of radiation. Most isotopic variations of selenium are stable, apart from ^{75}Se radioactive isotope emitting β and γ radiations. In nature, the most widespread isotope of the element is ^{80}Se.

1. 3. Occurrence of selenium in the environment

Selenium is a commonly occurring element in nature. It can be found in the atmosphere, lithosphere, biosphere, and hydrosphere of the Earth. This element circulating in the environment initiates the process of weathering in rocks [8]. Selenium is emitted into the atmosphere through volcanic gasses. Biomethylation of this element by microorganisms, decomposition of organic matter rich in this element, and so on contribute the most to the constant enrichment of the atmosphere with selenium. In these processes, volatile selenium compounds such as Dimethylselenium (DMSe), Hydrogen Selenide (H_2Se), and Selenium Oxide (SeO_2) are produced. The average selenium content in the arable layer of soil varies from 0.33 to 2 mg/kg on a global scale. Soils that have arisen from parent rocks rich in selenium such as sandstones and limestone have been reported to have selenium in large content [9].

In water, selenium is present in trace quantities, and mainly in the form of selenates and selenites. The amount of selenium in groundwater is much higher than that in seawater because of selenium elution from the parent rocks and excessive fertilization of soils with mixtures rich in selenium compounds [10]. The selenium content determined in groundwater in Poznań (Poland) is 0.17–0.44 μg/L. According to the recommendations of the World Health Organization (WHO), the acceptable amount of selenium in drinking water is 10 μg/L.

Selenium can be found in many minerals such as berzelianite (Cu_2Se), klaustalite (PbSe), and naumanite (Ag_2Se). It penetrates the soil as a result of anthropogenic activity through the combustion of coal and lignite, crude oil, and the use of agrotechnical processes—fertilization or liming.

1. 4. Occurrence of selenium in the human organism

Selenium is an essential bio-element that is necessary for the functioning of all organisms. The amount of this element present in nature and in the human organism is very diverse depending on the geographic region and diet. An optimal daily dose of this element is established at 55 μg and affects the normal course of biochemical and physiological processes [11]. Selenium is present in the human organism in trace quantities. Serum selenium levels may differ among populations, depending on a number of factors, including, but not limited to, concentration of selenium in food. The concentration of this element in adult human blood serum depends on a person's age.

The total amount of selenium in a human organism is ~3–20 mg. Skeletal muscles of the body are main organs containing ~46.9% of the total content of this element in humans, whereas kidneys contain only 4% of selenium. The most commonly used indicator of "selenium status" is the determination of its concentration in serum, which is estimated at 60–120 ng/mL. The maximum selenium concentration is achieved in adulthood. The content of this element in serum is progressively decreasing in individuals >60 years of age. In the human body, deficiency of this element is observed when its amount in plasma is lower than 85 μg/L. Low selenium concentration in plasma is associated with 4- to 5-fold increased risk of prostate cancer [12]. In the plasma of the residents of central Poland, selenium content is relatively low and is estimated to be ~50–55 μg/L.

For a long time, selenium was considered a toxic element. Poisoning with this element led to the development of severe anemia, bone stiffness, hair loss, and blindness. These symptoms have been observed in humans and animals in areas where the content of this element in the soil was ~1000 times greater in comparison with soils with an average amount of

selenium in the other regions of the world [13]. Selenium can also enter the body by inhalation; hence, its maximum concentration in the air should not exceed 0.2 mg/m^3. It should be emphasized that either too high level of selenium or its deficiency is harmful to human health.

The difference between a dose necessary for the proper functioning of the organism and a harmful dose is small. The recommended daily dose of selenium is different depending on the geographical area. The World Health Organization (WHO) recommends a daily dose of selenium at a level of 55 μg for adults. A daily dose of 400 μg is considered harmless [14]. Food and Nutrition Board (FNB) in the US has acknowledged that the amount of selenium needed changes with age and accounts for 40–70 μg for men and 45–55 μg for women. For children, the recommended daily dose should be 25 μg. In Great Britain, the recommended dose of selenium is higher in comparison with other parts of Europe, accounting for 60 μg for women and 75 μg for men

2. OCCURRENCE OF SELENIUM IN FOOD

In food, it is present in organic forms, exemplified by selenomethionine and selenocysteine. In dietary supplementation, the inorganic forms of selenium (selenite and selenate) are used [15]. Organic compounds are easily absorbed by human organisms in comparison with inorganic compounds.

Selenium food content is influenced by geographical location, seasonal changes, protein content and food processing. Periodic monitoring of selenium in food and soil is very important [16]. Diet is the major selenium source and approximately 80% of dietary selenium is absorbed depending on the food consumed. Selenium bioavailability varies according to the selenium source and nutritional status of the subject, being significantly higher for organic forms of selenium.

2. 1. Mechanism of selenium

Selenium displays several different mechanisms of action. Many of the various effects of selenium involve the incorporation of selenium into different proteins to create selenoproteins [17]. There at least 25 selenoproteins within human tissues that provide different functions in the body.

Selenium serves as a cofactor for glutathione peroxidase and helps minimize oxidative damage through cellular metabolism [18]. Selenium, in combination with vitamin E, protects cell membranes and organelles from peroxidative destruction. Thus, selenium can boost host defense and, ultimately, the immune system. Selenium's necessity in the endocrine system is defined by its role in making active thyroid hormone. The mineral interacts with iodothyronine deiodinase, an enzyme that transforms inactive thyroid hormone (T4) into active thyroid hormone (T3). As a dermatologic treatment, selenium in the form of selenium sulfide plays an alternative role with several suggestive mechanisms [19]. In the treatment of seborrheic dermatitis, dandruff, and tinea versicolor, selenium sulfide acts as an anti-pityrosporum agent that inhibits the growth of the fungus. Selenium sulfide's cytostatic effect on the epidermis lowers the mitotic rate and cell turnover in the basal layer, consequently reducing the production rate of the stratum corneum and limiting keratotic development. Selenium sulfide blocks enzymes involved in the growth of epithelial tissue. Lastly, research shows that selenium sulfide increases the rate of sebum excretion [20].

2. 2. Sources of selenium in the diet

Selenium is accumulated in the human organism to the largest extent mainly through ingestion. The products of plant and animal origin are the main sources of this element. Plants accumulate selenium in the form of inorganic compounds, selenates (IV) or (VI), which are then converted into organic forms, in particular selenomethionine and selenocysteine [21]. Selenocysteine dominates in the products of animal origin. This is the form in which selenium is consumed by humans, where further conversion of this element occurs, it is bound to amino acids and proteins. The amount of selenium in the diet is diverse and depends on the location in which plants were growing and animals were living [22]. It is determined by the amount of selenium in the soil in a given area, soil type, agro-climatic conditions, and the type of crop on the geographical region.

The bioavailability of selenium is dependent on many factors, of which the main factor is attributed to the chemical form of this element [23]. Selenium is most easily absorbed in the form of organic compounds and in the presence of vitamins A, D, and E. Bioavailability of selenium contained in foods is also determined by dietary factors such as fat, protein, and heavy metals content.

Brazil nuts, seafoods, and organ meats are the richest food sources of selenium. Other sources include muscle meats, cereals and other grains, and dairy products. The amount of selenium in drinking water is not nutritionally significant in most geographic regions. The major food sources of selenium in the American diet are breads, grains, meat, poultry, fish, and eggs.

The amount of selenium in a given type of plant-based food depends on the amount of selenium in the soil and several other factors, such as soil pH, amount of organic matter in the soil, and whether the selenium is in a form that is amenable to plant uptake [24]. As a result, selenium concentrations in plant-based foods vary widely by geographic location.

Protein rich foods were found to contain higher levels of selenium, whereas low levels were found in plants containing low protein. The main sources of selenium in the diet are foods for example, cereals, meat and dairy products, fishes, seafood, milk, and nuts. A rich source of selenium is found in the sea salt, eggs (only in case of Se-yeast supplementation of feed), giblets, yeast (yeasts containing selenium), bread, mushrooms, garlic, asparagus, kohlrabi (enriched with this element). Fruits and vegetables are characterized by a relatively low selenium content. It primarily occurs in the protein fraction, so that plants and vegetables containing a small amount of protein are a poor source of selenium [25]. A large content of selenium can be found in plants (hyperaccumulators), e.g., *Astragalus bisulcatus* and several representatives of *Brassicaceae*. Food products of animal origin are characterized by a diverse amount of selenium, depending on the geographical area in which the animals lived and the supply of selenium in the diet.

Table 2. Selenium Content of Selected Food

Food	Micrograms(mcg) per serving	Percent DV*
Brazil nuts, 1 ounce (6–8 nuts)	544	989
Tuna, yellowfin, cooked, dry heat, 3 ounces	92	167

Halibut, cooked, dry heat, 3 ounces	47	85
Sardines, canned in oil, drained solids with bone, 3 ounces	45	82
Ham, roasted, 3 ounces	42	76
Shrimp, canned, 3 ounces	40	73
Macaroni, enriched, cooked, 1 cup	37	67
Beef steak, bottom round, roasted, 3 ounces	33	60
Turkey, boneless, roasted, 3 ounces	31	56
Beef liver, pan fried, 3 ounces	28	51
Chicken, light meat, roasted, 3 ounces	22	40
Cottage cheese, 1% milkfat, 1 cup	20	36
Rice, brown, long-grain, cooked, 1 cup	19	35
Beef, ground, 25% fat, broiled, 3 ounces	18	33
Milk, 1% fat, 1 cup	8	15
Yogurt, plain, low fat, 1 cup	8	15
Lentils, boiled, 1 cup	6	11
Bread, white, 1 slice	6	11
Spinach, frozen, boiled, ½ cup	5	9
Spaghetti sauce, marinara, 1 cup	4	7
Cashew nuts, dry roasted, 1 ounce	3	5
Corn flakes, 1 cup	2	4
Green peas, frozen, boiled, ½ cup	1	2
Bananas, sliced, ½ cup	1	2
Potato, baked, flesh and skin, 1 potato	1	2
Peach, yellow, raw, 1 medium	0	0
Carrots, raw, ½ cup	0	0
Lettuce, iceberg, raw, 1 cup	0	0

Marine fishes caught in the north-western area of the Atlantic Ocean contain more selenium (168–825 μg/g) in comparison with freshwater fishes from of west part of the US (143–576 μg/g). Selenium content in chicken eggs is affected to the greatest extent by the diet of hens. Selenium in the egg yolk is present as a phosphoavidin—bound form, whereas in hen's egg as ovalbumin—bound form [26]. The same products originating from different countries contain different concentrations of selenium. Modified milk for children contains almost four times lesser selenium in comparison with human milk. As a result of feeding infants with modified milk, ~3.5 μg of selenium is daily introduced into the organism, whereas breastfed babies intake ~13.3 μg of this element from the mother's milk.

Cereal products cover ~50% of the daily intake of selenium, whereas the proportion of meat, poultry, and fishes accounts for ~35%. Water and drinks provide 5–25% of selenium. The portion of fruit in meeting the demand for selenium is relatively small and is <10%. Fresh and thermally untreated vegetables provide ~11% of selenium in a properly balanced diet. Thermal processing of food products can lead to loss of selenium in the food because of the formation of volatile selenium compounds [27]. These losses are significant and can reach tens of percent. Bioavailability of selenium in food is dependent on the form of its occurrence and the content of such compounds as protein, fat, and heavy metals. The bioavailability of selenium is reduced in the presence of heavy metals and sulfur but increases in the presence of vitamins A, C, E, and low-molecular-weight proteins containing methionine [28].

2. 3. Selenium supplementation

The primary source of selenium is the appropriately selected and balanced diet, covering the demand for this element. Selenium deficiency in healthy individuals results from a low content of this element in food or consumption of products with poor selenium content. It should be emphasized that the proportion of selenium present in a daily dose of individual food products is diverse [29]. Due to the widespread deficiency of selenium in humans, the need for supplementation of this element calls attention. Introduction of this element into the human body can occur indirectly, through the addition of selenium to fertilizers or fodder used to feed animals. Among direct supplementation methods, we can include the use of food supplements containing vitamins and micronutrients [30].

A country that introduced selenium supplementation due to a low concentration of selenium in the environment and too low supplementation of this element in the diet of people was Finland. Effects of selenium supplementation can be observed after a few weeks. They are dependent on the degree of deficiency of selenium in the organism, its dose, and chemical form. The reaction of the organism is more quickly noticed for supplementation of the organic form: selenomethionine in comparison with inorganic forms of selenium [31]. The most direct supplementation method is an individual use of properly enriched food supplements usually in the form of preparations, with in inorganic source of selenium or supplements based on selenium yeast biomass. Higher bioavailability and greater safety of preparations containing organic selenium differ from those with a content of inorganic selenium salts [32]. Additional advantages are low cost and simple manufacturing process of yeast biomass rich in selenium. Accordance with EU regulations the production of dietary supplements containing selenium may utilize dietary supplements in the form of selenium-enriched yeasts (<2500 μg S/g).

Selenomethionine, which is a dominant form in selenium yeast formulations, consists of a source of selenium in proteins; therefore, its use is a preferred strategy in preventing from deficiencies of this element in humans and animals [33]. In contrast, preparations containing

inorganic forms as sodium selenite may be more beneficial in clinical procedures (in cancer), in which fast effect is a priority. The use of supplements containing organic selenium of yeast origin, in case of deficiency, exhibits a multidirectional beneficial effect on human health. An interesting supplementation strategy is to use functional food products. These can be products obtained from selenium-enriched plant biomass [34].

Fermented foods contain lactic acid bacteria accumulating significant quantities of selenium, similar to yeast. Selenium supplementation in diet is recommended in the treatment of pancreatitis, infertility, and asthma. Reduced supply of selenium occurs also during other diet-related diseases. This relates to parenterally fed patients with mal-absorption and those suffering from metabolic diseases. Patients undergoing a specialized chemical treatment and after radiotherapy are also at risk of selenium deficiency [35]. Selenium deficiencies may be treated by the use of appropriately balanced pharmaceutical preparations (medicines) and dietary supplements that include selenium. These preparations are available without prescription. Selenium contained in these formulations may be present in organic form, for example, selenomethionine, or in the inorganic form of selenites (IV) and selenates (VI). Commonly available preparations are characterized by multidirectional action. Apart from supplementing the deficiency of selenium, they have a beneficial effect on the cardiovascular system and thyroid function. It positively affects the process of treatment of cardiovascular diseases and potentially reduces the risk of developing certain types of cancer [36].

Selenium in the forms of both inorganic compounds (Na_2SeO_3 and Na_2SeO_4) and organic ones (selenocysteine, selenomethionine, and selenoglutathione) introduced into the organism through food or drinking water results in a significant reduction of chemically induced cancers. Protective effect of selenium occurs after crossing a threshold amount in a diet, which corresponds to a dose of 250–300 μg Se/day. From health-improving viewpoint, it is important that a protective effect occurs in organs that are the main locations of tumors in humans (stomach, intestine, mammary gland, and liver).

It has been demonstrated that supplementation of fodder with selenium effectively protects against the increase of blood pressure in animals regularly exposed to heavy metal poisoning. Selenium supplementation reduces necrotic lesions in the testis and in animal fetus. In animals exposed to adverse effects of mercury compounds increased amounts of selenium reduce the formation of necrotic lesions in kidneys [37]. Selenium plays a role of chelating agent of heavy metals by the formation of toxic selenium–metal complexes. The most valuable and safe supplementation is the one that uses preparations containing selenium yeast. Their use has a multidirectional and beneficial effects on human health. Organic selenium derived from yeast has a better bioavailability in comparison with their inorganic forms. The use of selenium yeast on a large scale can help to reduce the deficiencies of this element resulting from a diet with low selenium content [38].

Fear against the introduction of selenomethionine (SeMet) into proteins, which could lead to the achievement of toxic levels of selenium, is not justified because of the natural equilibrium established, which prevents the uncontrolled accumulation of selenium in the organism. Furthermore, the release of SeMet from proteins through metabolic processes that occur during the disease should not result in toxic effect of selenium, because, until now, the mechanism that could be responsible for the selective release of SeMet during catabolism has not been identified [39].

Attention is paid to alternative forms of supplementation. In addition to yeast, biomass of bacteria and plants can also be enriched in selenium. Fermenting lactic acid bacteria supports

excessive accumulation of selenium; thus, the concept of using microorganisms for the production of functional food is justified. Research is being conducted on obtaining plants enriched in selenium and thus the possibility of obtaining protein fractions and selenium-enriched food products from them [40]. Many plants are a poor source of selenium; however, they exhibit the ability to accumulate this element in the cultivation and convert it to appropriate forms, thus becoming its potential reservoir.

Selenium supplementation has a very low adverse effect profile. A majority of the adverse reactions center around selenium sulfide. The more common adverse effects include redness, burning, itching, stinging, scalp sores, increased oiliness, nail hyperpigmentation, and irritation of the skin, creating contact dermatitis. Less common effects associated specifically with selenium sulfide shampoo include scalp hyperpigmentation, scalp discoloration, and alopecia. A rare non-dermatologic effect includes nausea due to the odour of the medication.

2. 4. Effect of excess selenium in the diet

Chronically high intakes of the organic and inorganic forms of selenium have similar effects. Early indicators of excess intake are a garlic odour in the breath and a metallic taste in the mouth. The most common clinical signs of chronically high selenium intakes, or selenosis, are hair and nail loss or brittleness. Other symptoms include lesions of the skin and nervous system, nausea, diarrhea, skin rashes, mottled teeth, fatigue, irritability, and nervous system abnormalities [41].

As discussed earlier, Brazil nuts contain very high amounts of selenium (68–91 mcg per nut) and could cause selenium toxicity if consumed regularly. Acute selenium toxicity has resulted from the ingestion of misformulated over-the-counter products containing very large amounts of selenium. In 2008, for example, 201 people experienced severe adverse reactions from taking a liquid dietary supplement containing 200 times the labeled amount [42]. Acute selenium toxicity can cause severe gastrointestinal and neurological symptoms, acute respiratory distress syndrome, myocardial infarction, hair loss, muscle tenderness, tremors, light-headedness, facial.

2. 5. Groups at risk of selenium inadequacy

The following groups are among those most likely to have inadequate intakes of selenium.

2. 5. 1. People undergoing kidney dialysis

Selenium levels are significantly lower in patients undergoing long-term hemodialysis than in healthy individuals. Hemodialysis removes some selenium from the blood. In addition, hemodialysis patients are at risk of low dietary selenium intakes due to anorexia resulting from uremia and dietary restrictions [43]. Although selenium supplementation increases blood levels in hemodialysis patients, more evidence is needed to determine whether supplements have beneficial clinical effects in these individuals.

2. 5. 2. People living with HIV

Selenium levels are often low in people living with HIV, possibly because of inadequate intakes (especially in developing countries), excessive losses due to diarrhea, and mal-absorption. Observational studies have found an association between lower selenium concentrations in people with HIV and an increased risk of cardiomyopathy, death, and, in

pregnant women, HIV transmission to offspring and early death of offspring [44]. Some randomized clinical trials of selenium supplementation in adults with HIV have found that selenium supplementation can reduce the risk of hospitalization and prevent increases of HIV-1 viral load; preventing HIV-1 viral load progression can lead to increases in numbers of CD4 cells, a type of white blood cell that fights infection. However, one trial showed that selenium supplementation in pregnant women can prevent early death in infants but has no effects on maternal viral load or CD4 counts.

2. 6. Recommended intake of selenium

Intake recommendations for selenium and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine of the National Academies (formerly National Academy of Sciences). DRI is the general term for a set of reference values used for planning and assessing nutrient intakes of healthy people [45]. These values, which vary by age and sex, include:

- Recommended Dietary Allowance (RDA): Average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals; often used to plan nutritionally adequate diets for individuals.
- Adequate Intake (AI): Intake at this level is assumed to ensure nutritional adequacy; established when evidence is insufficient to develop an RDA.
- Estimated Average Requirement (EAR): Average daily level of intake estimated to meet the requirements of 50% of healthy individuals; usually used to assess the nutrient intakes of groups of people and to plan nutritionally adequate diets for them; can also be used to assess the nutrient intakes of individuals.
- Tolerable Upper Intake Level (UL): Maximum daily intake unlikely to cause adverse health effects.

Table 3 lists the current RDAs for selenium in mcg. For infants from birth to 12 months, the FNB established an adequate intake for selenium that is equivalent to the mean intake of selenium in healthy, breastfed infants.

Table 3. Recommended Dietary Allowances (RDAs) for Selenium

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months	15 mcg*	15 mcg*		
7–12 months	20 mcg*	20 mcg*		
1–3 years	20 mcg	20 mcg		
4–8 years	30 mcg	30 mcg		
9–13 years	40 mcg	40 mcg		
14–18 years	55 mcg	55 mcg	60 mcg	70 mcg

19–50 years	55 mcg	55 mcg	60 mcg	70 mcg
51+ years	55 mcg	55 mcg		

2. 7. Importance of selenium

Selenium is a powerful mineral that is essential for the proper functioning of your body. It plays a critical role in metabolism and thyroid function and helps protect your body from damage caused by oxidative stress. Selenium may help boost the immune system, slow age-related mental decline, and even reduce the risk of heart disease [46]. This micronutrient can be found in a wide variety of foods, from oysters to mushrooms to Brazil nuts. Adding more selenium-rich foods to your diet is an excellent way to maintain good health.

2. 8. Deficiency of selenium

Selenium deficiency produces biochemical changes that might predispose people who experience additional stresses to develop certain illnesses [47]. For example, selenium deficiency in combination with a second stress (possibly a viral infection) leads to Keshan disease, a cardiomyopathy that occurred in parts of China prior to a government-sponsored selenium supplementation program that began in the 1970s. Before the Chinese government supplementation program, adults in the Keshan disease areas had average selenium intakes of no more than 11 mcg/day; intakes of at least 20 mcg/day protect adults from Keshan disease.

Selenium deficiency is also associated with male infertility and might play a role in Kashin-Beck disease, a type of osteoarthritis that occurs in certain low-selenium areas of China, Tibet, and Siberia. Selenium deficiency could exacerbate iodine deficiency, potentially increasing the risk of cretinism in infants [48].

Selenium deficiency is often a population-level problem rather than an individual one. It affects a community as a whole. Biofortification has been the approach used to tackle this problem by fertilizing the soil at the agricultural end of things. Alternately enrichment of food sources through fodder with selenium compounds, for instance, eggs (or rather, egg yolks) with more selenium, is also another approach that has been used to raise nutritional selenium content [49]. In many countries, eggs, meat, and milk fortified with selenium have been introduced successfully. Using microorganisms for the production of functional foods such as selenium yeast is yet another approach that is being used. Organic selenium is less likely to reach toxic levels as quickly as supplementing with selenite and selenate (the inorganic salt forms of selenium supplements) can.

However, using inorganic salts is a quick way to supplement selenium in the situation of gross and immediate deficiency. The goal to target is supplementation, achieving about 90 mcg/day for adults. Per the World Health Organization, the tolerable upper intake level for selenium in adults 19 years or older is 400 micrograms or 5.1 micromoles per day [50]. Levels above this are considered toxic. Ultimately, a balanced diet is the best way to stave off selenium deficiency.

Symptoms of selenium deficiency are rare but include:

- Deformity of bones, cartilage, and joints
- Restricted movements
- Myalgias

- Extremity edema
- Shortness of breath

Selenium level can be monitored via:

- Serum selenium levels
- Scalp hair selenium levels
- Nail selenium levels
- Glutathione peroxidase activity in plasma
- Glutathione peroxidase activity in erythrocytes
- Glutathione peroxidase activity in thrombocytes
- Glutathione peroxidase activity in whole blood
- The concentration of selenoprotein P (SePP)

3. SELENIUM TOXICITY

Selenium is considered a relatively non-toxic supplement. However, extremely high selenium intake can result in diarrhea, fatigue, hair loss, joint pain, nail discoloration or brittleness, and nausea. Due to selenium supplementation toxicity being extremely rare, there is no current treatment for selenium overdose [51]. If selenium toxicity is suspected, it is best to stop using the supplement. The symptoms of selenium toxicity depend on the route of exposure.

Inhalation and Ingestion of selenium

The inhalation of selenium compounds causes respiratory membrane irritation, pulmonary edema, bronchial inflammation, and pneumonia. Elemental selenium dust exposure also produces mucous membrane irritation, bleeding from the nose, and coughing, among other symptoms [52]. Other features include vomiting and nausea, cardiovascular effects, headaches and malaise, and ophthalmic irritation.

The long-term intake of excessive selenium may involve either organic or inorganic forms in food and/or water. The symptoms of chronic selenium toxicity or selenosis first appear as a garlicky odour in the breath and a metallic taste in the mouth. This is followed by gastrointestinal symptoms such as nausea or diarrhea, tiredness, irritability, and joint pain, all of which occur in approximately 70-75% of patients. Other characteristic features include loss of mentation, paresthesia, hyper-reflexia, nail changes resulting in brittleness, deformation, and loss of nails, alopecia, discoloration and loss of teeth, as well as skin rashes [53]. These are seen in more than 60-65% of patients.

Acute selenium toxicity

Acute toxicity presents with acute respiratory distress syndrome, myocardial infarction, renal failure, vascular symptoms such as tachycardia and flushing of the face, as well as neurological features including tremors, irritability, and myalgia [54]. Echocardiogram (ECG) abnormalities such as T-wave inversion and QT prolongation are often seen, with death often occurring as a result of refractory hypotension

3. 1. Causes of selenosis

Causes of selenosis range from ingestion of excessive selenium, as is the case of regular snacking on Brazil nuts which could contain up to 90 μg of selenium per nut. There are also many other plants that have the capability to concentrate selenium that is taken up from the soil, which are termed selenium accumulators [55]. In contrast to the normal plant's selenium content of 10 part per million (ppm), even when they grow on selenium-rich soil, selenium accumulators may have concentrations in thousands of ppm. For example, *Astragalus racemosus* was reported to have a concentration of almost 15,000 ppm of selenium. These plants are able to grow only on seleniferous soils and are therefore called primary selenium indicators. While found largely in North America, some species do grow in Australia. Other selenium accumulators also exist, which can grow on selenium-poor soils and are referred to as secondary soil accumulators.

3. 1. 1. Toxic selenium compounds

The most toxic compound of selenium following inhalation is hydrogen selenide. Other toxic compounds include selenium dioxide, sodium selenite, and selenium sulfide. Sodium selenite is the most toxic compound when ingested orally.

Selenium sulfide has been linked with the occurrence of liver and lung tumors in mice and rats following oral exposure [56]. As a result, selenium sulfide is a Group B2 carcinogen as per the United States Environmental Protection Agency (EPA) classification. Elemental selenium has low toxicity following oral administration.

The EPA has also classified elemental selenium as a Group D carcinogen, which indicates that it is not classifiable as a human carcinogen.

3. 1. 2. Causes of selenium toxicity

Exposure to selenium primarily occurs through food, and in some areas with seleniferous soils, through drinking water [57]. Airborne exposure is rare; however, occupational exposure is possible with the chemical processes for recovery of selenium, painting trades, and the metal industries.

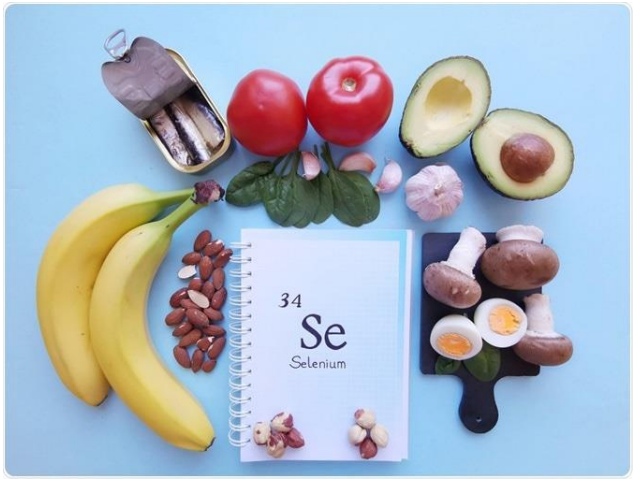

Figure 2. Causes of selenium toxicity

Gun-bluing chemicals contain a high concentration of selenium and are often involved in acute poisoning. Potential sources of toxic levels of selenium include Astragalus and copper ingestion.

3. 1. 3. Toxic levels of selenium

Some agencies have put forward a chronic reference exposure level of 0.02 mg/m^3 for selenium and its compounds, as well as 0.00008 mg/m^3 for hydrogen selenide. These values have been determined based on findings in humans with selenosis and guinea pigs with selenium inhalation toxicity [58].

3. 1. 4. Interactions between selenium and other medications

Selenium may exacerbate the effects of:

- Anticoagulants
- Sedatives
- Herbs that impair coagulation such as angelica, cloves, and ginger.

Selenium may impair the effects of:

- Immunosuppressants
- Oral contraceptives
- Cholesterol-lowering agents
- Niacin
- Copper supplements

Supplements that lower the efficacy of selenium:

- Gold salts
- Omega-3 fatty acids
- Zinc

3. 2. Selenium and diseases

3. 2. 1. Selenium and cancer

Studies of selenium levels and large populations over time have found a correlation between people who eat a lot of selenium and a lower risk of some cancers, specifically bladder cancer, prostate cancer, lung cancer and some gastrointestinal cancers. More than 100 small animal experiments have shown selenium supplements reduce the number of new tumors, according to a January 2004 review published in the British Journal of Nutrition.

Regions with selenium-rich soil tend to have lower death rates from cancer than areas with low-selenium soil, particularly for cancers of the lung, esophagus, bladder, breast, colon, rectum, pancreas, ovary and cervix, according to the American Cancer Society [58]. But these trends do not prove selenium is an underlying factor in cancer survival.

Controlled studies, in which groups of people were given either selenium supplements or a placebo, have found conflicting results about selenium's cancer fighting properties.

A study of more than 1,300 men and women with non-melanoma skin cancer found that the group of men assigned to take selenium supplements also had 52 percent fewer cases of

prostate cancer, according to the 2003 paper published in the journal BJUI. But a larger study of more than 35,000 men called the Selenium and Vitamin E Cancer Prevention Trial (SELECT), found selenium supplements had no influence on prostate cancer risk.

3. 2. 2. Selenium and heart disease

Preliminary studies show selenium may play a role in heart health. Selenium reduces inflammation and prevents platelets a type of clotting cell in the blood from aggregating, which is necessary for blood clots to form. Blood clots can lead to stroke, heart attacks, kidney failure, pulmonary embolism and other problems [59].

A selenium deficiency may make atherosclerosis (a hardening of the arteries) worse. Animal studies have shown supplementing selenium after a long dietary deficiency reversed cardiovascular damage in mice. However, human studies on the subject have seen mixed results.

Some observational studies, where doctors track people but don't randomly assign them to taking a supplement or a placebo, found that the lower the selenium levels in the blood, the higher a person's risk of high blood pressure and coronary heart disease [60]. But other observational studies didn't find a significant link between selenium levels and cardiovascular disease. Some observational studies even found the opposite trend; higher selenium levels were associated with worse cardiovascular health, according to the National Institutes of Health (NIH).

In one clinical trial, researchers assigned more than 450 older adults to take either a placebo or various strengths of selenium supplements for six months. They found the people taking selenium supplements had lower levels of bad cholesterol, and the group taking the highest amount of selenium (300 micrograms) also showed higher levels of HDL ("good") cholesterol, according to a May 2011 paper in the Annals of Internal Medicine.

However, a 2012 review by the Cochrane Collaboration concluded that taken together, the evidence from selenium studies including nearly 20,000 people participating in 12 trials did not support taking selenium supplements as a way to prevent major cardiovascular disease. However, the researchers did note that the vast majority of participants were men from the United States, where people already get a lot of selenium from food.

3. 2. 3. Selenium and rheumatoid arthritis

People with rheumatoid arthritis are more likely to have low selenium levels, but it is currently unclear whether low selenium levels are a result of the condition, or a contributing factor [61]. Once a person is diagnosed with rheumatoid arthritis, selenium supplements do not seem to help, according to the University of Maryland Medical Center.

3. 2. 4. Selenium and memory loss

Because selenium levels decline with age, there is a possibility that selenium influences age-related mental decline. Large observational studies have found either no link between selenium levels and memory test scores, or found that people with lower selenium levels are more likely to have cognitive decline over time, according to the NIH.

One eight-year study of more than 4,000 participants, ages 45 to 60, found that people taking antioxidant supplements had better verbal memory scores six years after the study ended, according to the September 2011 paper in the American Journal of Clinical Nutrition. However,

because the antioxidant supplements included a mix of vitamin and minerals, the researchers could not separate what, if any, influence selenium had on memory scores. Selenium may have a role in cognitive decline because of its antioxidant properties, which can protect brain cells from damage over time [62]. But overall, the limited number of studies on selenium and mental decline do not provide enough evidence to determine whether selenium can influence brain function, according to the NIH.

3. 2. 5. Selenium and thyroid problems

Evidence supports a link between selenium levels, iodine deficiencies and thyroid function, especially in women. Selenium is more concentrated in the thyroid than in other organ in the body, and it is important in the production and metabolism of thyroid hormone.

One analysis of 1,900 people in France found that among women a mild iodine deficiency, those with lower the selenium levels were more likely to develop goitres or thyroid damage compared with those with higher selenium levels, according to a 2003 article in the European Journal of Endocrinology. Subsequent studies have found similar links [63]. However, controlled studies on thyroid health, where participants are given selenium supplements or placebos, have had mixed results. More research is needed to determine if selenium supplements can fight thyroid diseases.

3. 2. 6. Selenium and diabetes

There is limited research on selenium supplements and diabetes risk. A few large observational studies showed a correlation between higher selenium concentrations in toenails and a lower risk of diabetes [64].

However, a placebo-controlled study of more than 1,200 people over seven years found selenium supplements didn't reduce the risk of type 2 diabetes, and may actually increase diabetes risk, according to the 2007 paper published in the Annals of Internal Medicine.

3. 2. 7. Selenium and HIV

Selenium levels tend to drop as HIV infections progress. Recent studies on selenium supplements in HIV-positive patients show some promise. One laboratory study of human blood cells found that adding a certain selenoprotein to HIV-infected cells slowed the replication of HIV by 10-fold, compared with HIV-infected human cells without the selenoprotein, according to the November 2008 paper in the Journal of Biological Chemistry.
A study on 878 HIV-positive people in Botswana, who had not taken antiretroviral medicines, showed a multivitamin in combination with selenium supplements slowed the progression of HIV symptoms and lowered the risk of death, according to the November 2013 paper published in the Journal of the American Medical Association. Interestingly, the selenium supplements alone or the multivitamin alone did not provide any better protection than placebo during the two-year study. Another controlled study of HIV-positive people found that 200 micrograms of daily selenium supplements could suppress HIV viral burden (the amount of virus in the blood) and strengthen the immune system [65].

3. 2. 8. Selenium and Cardiovascular disease

Selenoproteins help prevent the oxidative modification of lipids, reducing inflammation and preventing platelets from aggregating. For these reasons, experts have suggested that

selenium supplements could reduce the risk of cardiovascular disease or deaths associated with cardiovascular disease. The epidemiological data on the role of selenium in cardiovascular disease have yielded conflicting conclusions. Some observational studies have found an inverse association between serum selenium concentrations and risk of hypertension or coronary heart disease. A meta-analysis of 25 observational studies found that people with lower selenium concentrations had a higher risk of coronary heart disease [66]. However, other observational studies failed to find statistically significant links between selenium concentrations and risk of heart disease or cardiac death, or they found that higher selenium concentrations are associated with an increased risk of cardiovascular disease.

Several clinical trials have examined whether selenium supplementation reduces the risk of cardiovascular disease. In one randomized, placebo-controlled study, for example, 474 healthy adults aged 60 to 74 years with a mean baseline plasma selenium concentration of 9.12 mcg/dL were supplemented with 100, 200, or 300 mcg selenium per day or placebo for 6 months. The supplements lowered levels of total plasma cholesterol and non–high-density-lipoprotein (HDL) plasma cholesterol (total cholesterol levels minus HDL levels) compared with the placebo group, whereas the 300 mcg/day dose significantly increased HDL levels. Other trials have provided evidence that selenium supplementation (200 mcg/day) or supplementation with a multivitamin/multimineral pill containing selenium (100 mcg/day) does not reduce the risk of cardiovascular disease or cardiac death. A review of trials of selenium-only supplementation for the primary prevention of cardiovascular disease found no statistically significant effects of selenium on fatal and nonfatal cardiovascular events [67].

The limited clinical-trial evidence to date does not support the use of selenium supplements for preventing heart disease, particularly in healthy people who already obtain sufficient selenium from food. Additional clinical trials are needed to better understand the contributions of selenium from food and dietary supplements to cardiovascular health.

3. 2. 9. Selenium and Cognitive decline

Serum selenium concentrations decline with age. Marginal or deficient selenium concentrations might be associated with age-related declines in brain function, possibly due to decreases in selenium's antioxidant activity [68].

Researchers have evaluated whether taking an antioxidant supplement containing selenium reduces the risk of cognitive impairment in elderly people. An analysis of data from the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study on 4,447 participants aged 45 to 60 years in France found that, compared with placebo, daily supplementation with 120 mg ascorbic acid, 30 mg vitamin E, 6 mg beta-carotene, 100 mcg selenium, and 20 mg zinc for 8 years was associated with higher episodic memory and semantic fluency test scores 6 years after the study ended. However, selenium's independent contribution to the observed effects in this study cannot be determined [69]. More evidence is required to determine whether selenium supplements might help prevent or treat cognitive decline in elderly people.

3. 2. 10. Selenium and other health conditions

People with asthma tend to have lower selenium levels than people without asthma. It has not been found that taking selenium supplements can reduce asthma symptoms, according to the University of Maryland Medical Center. And while selenium is needed to make healthy

sperm, very high selenium levels are also linked to decreased sperm motility. Selenium does help the production of white blood cells, which help fight infection. It has not been known whether selenium supplements beyond the recommended daily amount boost the immune system.

4. TREATMENT FOR SELENIUM TOXICITY

For the present purposes, toxicity is characterized as acute or chronic. Acute poisoning typically involves a single dose that produces symptoms within min to hr, whereas chronic poisoning involves smaller doses given repeatedly, producing symptoms that become apparent over days or longer. Selenium toxicity is determined on the basis of signs and symptoms in the individual subject, not by laboratory values. The strong garlic-like odour usually present in both acute and chronic poisoning is attributed to the volatile metabolite dimethylselenide [70]. This odour has also been described in the breath of individuals with sub-toxic exposure.

Different chemical forms of selenium can have vastly different toxic potentials. For example, when given orally to rats, the average lethal dose (LD_{50}) was 7 mg Se/kg body weight for sodium selenite, 138 mg Se/kg for selenium sulfides (as formulated for anti-dandruff shampoos), and 6700 mg Se/kg for elemental selenium.

4. 1. Acute pattern.

Early signs of acute toxicity include hypotension and tachycardia. Early cardiac abnormalities often show T-wave flattening and inversion, and a prolonged QT interval. Death is typically preceded by refractory hypotension from peripheral vasodilatation and direct myocardial depression. Nausea, vomiting, diarrhea, and abdominal pain are often present, and pulmonary edema can be a serious complication [71]. Neurologic symptoms may include tremor, muscle spasms, restlessness, confusion, delirium, and coma. Ingestion of caustic compounds such as selenious acid often causes mucosal damage to the oral cavity, esophagus, and stomach. Laboratory abnormalities include elevated serum creatine kinase (CK) acivity, often appearing early and peaking at 4–5 days; the MB fraction of CK typically remains low.

4. 2. Gun-bluing

Acute selenium poisoning often involves a commercial product used to stain metal a traditional gun-metal blue color. These gun-bluing agents typically contain formulations such as 2-9% selenious acid and 2–4% copper (II) in dilute acid [72]. Although they are relatively high in copper and have sufficient acid to damage mucous membranes, the primary toxic agent is selenium.

4. 3. Chronic pattern.

Chronic selenium poisoning, or selenosis, often presents with nail changes and alopecia. Other features may include nausea, vomiting, diarrhea, fatigue, and skin lesions. Peripheral paresthesias can be present, along with hyperreflexia and pain in the extremities. As selenosis progresses, decreased cognitive function, weakness, paralysis, and death can occur.

Nail changes are the most common sign of chronic selenium poisoning. The nails become brittle, and white spots and longitudinal streaks appear on the surface [73]. As chronic poisoning

becomes more severe, breaks in the nail occur and the nail can be lost; nails may grow back deformed and be lost repeatedly. Fragile nails and similar changes are obviously not specific for selenosis, and other causes include fungal infection, psoriasis, and arsenic exposure. Nail changes are also unlikely to be the sole evidence of chronic selenium poisoning [74]. When considering a patient with an elevated selenium concentration, the absence of characteristic nail changes is consistent with a lack of chronic poisoning.

4. 4. Treatment

Although the treatment of selenium poisoning is not reviewed here, several points are worth emphasizing [75]:

i. The most important aspects of treatment are supportive care and the prevention of further exposure,
ii. Chelation is not recommended since animal studies suggest it may increase toxicity,
iii. Emesis is not recommended, particularly if a caustic compound such as selenite is involved.

5. CONCLUSION

Selenium plays an important role in maintaining the homeostasis of the human body. The study of selenium has shown that it is a trace mineral needed in small quantity in the diet. The issue of selenium supplementation in order to prevent various disorders is still an open question and requires further research. Due to promising data from clinical trials, the use of supplementation of this element should be considered. An innovative product, an example of which may be dietary supplements enriched in selenium should be more adapted to the requirements of consumers. Selenium deficiency is linked to so many diseases, which part of it is Cancer mortality, HIV/AIDs. Selenium supplementation reduces rate of cancer.

Yeast enriched with organic selenium forms can be a good source of this ingredient to the consumer's diet. However, it should be remembered that every product should be precisely checked for the content of individual nutrients, safety, and correctness of action. Satisfying the sophisticated consumer needs with simultaneous supplementation of deficient elements can be an effective tool in the fight for health.

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