

The toxicity of different selenium forms and compounds – Review

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SUMMARY

Selenium (Se) is an unusual metalloid of considerable interest from both a toxicological and a nutritional perspective, with a very narrow safe range of intake. Although there are many reports about its detoxification properties, toxicity aspects of it have also been tracked for several decades. Lots of studies demonstrated that low Se is an efficacious avail whereas high Se can induce toxicity and the significant toxicity of selenium emphasizes the need to assess the health risk of various selenocompounds as nutritional supplements. The toxicity of different forms and compounds of selenium is also summarized in this review.

Keywords: toxicity, selenium form, selenium compound

ÖSSZEFOGLALÁS

A szelén (Se) egy nem szokványos félfém, mely iránt komoly érdeklődés mutatkozik mind toxikológiai, mind pedig táplálkozási szempontból. A szelén biztonságos beviteli mennyisége ugyanakkor nagyon korlátozott. Bár sokan vizsgálták a detoxifikációs tulajdonságait, a szelén toxikusságát szintén jónéhány évtizede kutatják. Számos tanulmány mutatott rá, hogy az alacsony szelénbevitel hatékony lehet, a nagyarányú bevitel azonban toxikus hatású, mely szükségessé teszi a különféle táplálékkiegészítőként alkalmazott szelénvegyületek egészségi kockázatának felmérését. Ez a tanulmány tartalmazza a szelén különféle formáinak és vegyületeinek toxicitási adatait is.

Kulcsszavak: toxicitás, szelénforma, szelénvegyület

INTRODUCTION

Selenium is a member of the non-metallic elements within group VIa of the periodic table. It has an atomic number of 34, an atomic weight of 78.96, and has six different naturally occurring stable isotopic masses from 74 to 82 (Rosman and Taylor, 1997). Selenium has four natural oxidation states: -2 (selenides), 0 (elemental), +4 (selenites), and +6 (selenates) (Barceloux, 1999). Selenium was first identified in 1817 by Jons Jakob Berzelius, a Swedish chemist, who investigated worker illnesses in a sulfuric acid plant at Gripsholm, Sweden (Fredga, 1972). He named this element after "Selene", the green moon Goddess.

Selenium toxicity was first confirmed in 1933 to occur in livestock that consumed plants of the genus *Astragalus*, *Xylorrhiza*, *Oonopsis*, and *Stanleya* in the western regions of the United States (Spallholz, 1994).

Cases of selenium poisoning are usually a result of one of three types of exposure history. First, grazing animals ingest forages that have accumulated selenium in higher concentrations than normal from seleniferous soils. Second, selenium toxicity is from environmental contamination from agricultural drain water, reclaimed soils from phosphate or ore mining, sewage sludge or fly ash. Third, selenosis is caused by accidental overdoses by injection of selenium supplements or by misformulation of feed mixes. Each of these poisoning may be observed subacute, acute or chronic selenosis depending on the daily dose and duration of exposure (Zane Davis and Hall, 2011).

TOXICITY OF SELENIUM FORMS AND COMPOUNDS

Elemental selenium is insoluble in aqueous media and is considered biologically inert. Elemental selenium and most metallic selenides have relatively less toxicity because of the low bioavailability, which on the other hand limited their utility in feed and food nutritional supplementation. By contrast, selenates, selenites and organoselenium compounds, such as selenomethionine (SeMet), selenocysteine and methylselenocysteine are widely used as nutritional selenium source but they are all toxic in higher doses. In general, SeMet and SeMet enriched yeast are more effective for increasing human and animal selenium levels and less toxic than inorganic selenium. The reason may lie on the non-specific incorporation of selenomethionine into proteins and providing reversible selenium storage in organs and tissues (Schrauzer, 2003).

However, the excessive incorporation can also lead to structural malformation or loss of enzymatic activity in some sulfur-containing proteins due to the replacement of sulfur in sulfhydryl groups or thiols (critical for disulfide bond formation) with selenium (Stadtman, 1990).

Se-methylselenocysteine (SeMC), another naturally occurring organoselenium compound was firstly identified in *Astragalus bisulcatus* (Trelease et al., 1960) and later found in many other plants (Lyi et al., 2005; Freeman et al., 2012), was reported to be less toxic and more bioactive than inorganic or other organic selenium compounds (Hoefig et al., 2011). Because SeMC is not readily incorporated into proteins and accumulates in a

free pool after ingestion, it has been considered a better form of nutritional selenium supplements (Neuhierl and Bock, 1996). In addition, recent studies indicated that SeMC conferred remarkable protection against breast cancer (Ip et al., 2000; El-Bayoumy and Sinha, 2004; Unni et al., 2005; Zhang and Zarbl, 2008), prostate cancer (Zhang et al., 2010; Sinha et al., 2014) and colorectal carcinoma (Cao et al., 2014). SeMC can be a similar or better selenium source than SeMet and supplies methylselenol, an active metabolite recognized essential for the anticancer effect (Ip et al., 2002; Zhan et al., 2013), much more efficiently in organs than SeMet (Suzuki et al., 2006). It is promising that SeMC can be developed as a pharmaceutical drug that can be used in chemoprevention and clinical intervention of human cancers. However, a common concern in the uses of SeMC either for nutritional supplementation or for cancer chemoprevention is the safety risk rising from significant toxicity of selenium, and this has not been well elucidated yet.

Two common inorganic forms of selenium (selenite and selenate) are important in biogeological and biochemical cycle of Se, but they have different biochemical properties. For example, their toxicity and energy consumption during uptake and metabolism are different (Shen et al., 1997; Weiller et al., 2004).

Selenite is generally more toxic than selenate in aquatic environment (Eisler, 2007). On the other hand, selenate proved to be more toxic than selenite to soil animals (Somogyi et al., 2007).

SELENIUM TOXICITY IN PLANTS

Selenium occurs in the earth's crust most commonly as selenite, selenate and selenides associated with sulphide minerals (NRC, 1983). Many factors dictate the concentration of selenium in plants including but not limited to the type of vegetation, chemical form of selenium in the soil, pH of soil, moisture content of soil and the concentration of selenium in the soil. Selenium is commonly found as water-soluble selenate in well-aerated, alkaline soils and is readily absorbed via the sulphate transporter system by plants, as compared to very poor uptake of selenides and selenite. Some soils also contain selenomethionine from decay of selenium containing vegetation which also is taken up by some plants (Marschner, 1995).

Soils containing high concentrations of selenium are commonly found in many parts of the world. Many areas within the Northern Great Plains of the United States, such as the Dakotas, Wyoming, Montana, Nebraska, and Kansas, have high soil selenium content (4–5 mg kg⁻¹ Selenium or more), resulting in high level of plant uptake and subsequent Se toxicosis in herbivores (Rosenfeld and Beath, 1964). Seleniferous soils are often characterized by alkaline soils that were developed from shales and are located in arid or semi-arid climates. In North America seleniferous soils and forages with high concentrations of selenium have been found in western Canada, Arizona, Colorado, Idaho, Kansas, Nevada, North Dakota, South Dakota, New Mexico and Oklahoma. High soil selenium also occurs in alkaline soils of some localities in Algeria,

Argentina, Australia, Bulgaria, Canada, China, Columbia, Ireland, Israel, Mexico, Morocco, New Zealand, South Africa, the former Soviet Union, Spain, and Venezuela (NRC, 1983). However, total soil selenium is not the best indicator of potential selenium poisonings, as Hawaii and Puerto Rico have areas of high soil selenium that is not available to the plants due to the acidic soil types, which result in lowered water soluble, bioavailable selenium for plant uptake (Lakin, 1961).

Areas that contain soils high in available selenium are often identified by the presence of obligate indicator plants that require high selenium for survival; including *Astragalus* spp., *Oenopsis* spp., *Stanleya pinnata* and *Xylorrhiza* spp.

Facultative selenium accumulator plants do not require high selenium for survival but can accumulate high selenium. Obligate selenium accumulator plants can store selenium at concentrations of 3000 to 10 000 mg kg⁻¹ selenium on a dry weight basis (Freeman et al., 2006), while facultative accumulator plants can contain several hundred to several thousand mg kg⁻¹, and non-accumulator plants growing on the same soil may contain from ten to occasionally a few hundred mg kg⁻¹. The majority of selenium in accumulator plants is found as organic methyl-selenocysteine and selenocystathionine or as inorganic selenate (Shrift and Virupaksha, 1965; Underwood and Suttle, 1999; Pickering et al., 2003; Freeman et al., 2006). The selenium in most plants that grow on normal soils contains <3 mg Se/kg with the predominant forms of selenium being selenate and selenomethionine (Whanger, 2002). Several chemical forms have been reported in non-indicator plants growing on high selenium soils.

Inorganic forms of selenium are the primary form in soil. Only the water soluble forms are readily available for plant uptake, with the greatest absorption being in the form of selenate via the sulfate transporter. Elemental selenium and precipitated metal-selenides are not bioavailable for plant uptake.

Briefly, about selenium metabolism in plants we should note that selenate for both accumulator and non-accumulator plants is less toxic and is absorbed to a greater extent than selenite, which is most toxic to the non-accumulator plants, the grains and grasses.

SELENIUM TOXICITY IN ANIMALS

Selenium toxicity in livestock is invoked by ingestion of both primary and secondary selenium accumulator plants containing moderate to high levels of selenium. Toxicity is manifested, as previously noted, in "alkali and blind staggers diseases." Experimental chronic selenium toxicity in animals is known to affect the major organs including the liver, spleen, kidneys, heart, and pancreas. Multiple factors contribute to chronic experimental selenium toxicity including animal species, dietary selenium compound administered, quality of dietary protein, dietary acclimation, and of course, dietary selenium concentration.

Experimental selenium toxicity has been most widely studied in rodents, but it has also been studied in other species of animals (Muth et al., 1967; Cooper

and Glover, 1974; Oldfield, 1987). Selenium toxicity in humans is rare, yet it occurs with symptoms similar to those found in animals (Combs et al., 1987; Neve and Favier, 1989). In the rat, the dietary requirement for selenium is ca. 0.20 mg kg⁻¹ (Hafeman et al., 1974). The threshold for selenium toxicity from selenite is about 0.50 mg kg⁻¹, a mere 2.5 times the dietary requirement (Tinsley et al., 1967). Chronic dietary selenite toxicity in the rat begins at 3–4 mg kg⁻¹ and there is almost no survival of rats fed 16 mg kg⁻¹ Se (Harr et al., 1967). Chronic ingestion of either selenite or selenate in the rat, at the same selenium dietary levels, exhibits nearly equivalent toxicity (Brasher and Ogle, 1993; Wilber, 1993). Dietary ingestion of organoselenium compounds, however, exhibit wide differences in toxicity.

In comparison to selenite, on an equivalent selenium basis, selenocystine toxicity is approximately equal to that of selenite (Martin and Hurlbut, 1976). Selenomethionine is less toxic than selenite with the L-isomer being only slightly more toxic than the D-isomer (Stewart et al., 1986; Choy et al., 1993). Se-methylselenocysteine, the nonproteinaceous amino acid found in selenium accumulator plants, exhibits reduced or delayed toxicity in mice (Martin and Hurlbut, 1976). Other selenoethers, dimethylselenide, trimethylselenonium ion, and selenobetaine are not very toxic in comparison to selenite (McConnell and Portman, 1952; Ip and Ganther, 1992).

WHY IS SELENIUM TOXIC?

1. Selenium compounds, i.e., selenite and selenium dioxide, can react with glutathione (GSH) and other thiols to form selenotrisulfides that will ultimately react to produce superoxide and hydrogen peroxide, and are toxic.
2. Diselenides, i.e., selenocystine and selenocystamine in the presence of GSH and other thiols, are reduced to selenols (RSeH), which are catalytic, produce superoxide and hydrogen peroxide, and are toxic.
3. Selenium compounds that do not react with thiols, i.e., selenate and all tested selenoethers (RSeR), do not produce superoxide or hydrogen peroxide in vitro and are not toxic per se.
4. Selenate and selenoethers are toxic in tissue culture or in vivo only after being reduced to selenite or a selenol.
5. Selenium toxicity manifests itself acutely or chronically when oxidative damage exceeds antioxidant defenses or the ability of either plants or animals to form selenoproteins, selenoethers, or elemental selenium (Se⁰) (Spallholz, 1994).

SELENIUM NUTRITIONAL TOXICITY

Different chemical forms of selenium are highly toxic. From a nutritional aspect, systemic toxicity implies that selenium is bioavailable from the chemical form under consideration, which is the case for selenite, selenate and selenoamino acids, i.e. selenomethionine (Se-methionine)

and Se-cystine (Levander, 1983). Sodium selenite is resorbed by passive diffusion, while the absorption of sodium selenate from the intestinal brush border is an active transport, where the corresponding sulfur compounds can compete (Arduser et al., 1985; Wolfram et al., 1988; Wolfram, 1995). The rate-limiting step for the bioavailability of selenium, however, is not the rate of resorption, but the conversion into a metabolically active form (Contempre et al., 1996). First of all, in an intracellular environment, sodium selenite undergoes a spontaneous reaction with abundantly present reduced glutathione to form seleno-diglutathione with a stoichiometry of 1:4 between selenite and glutathione (Ganther, 1968).

In a secondary reaction, seleno-diglutathione is converted to seleno persulfide (GSSeH) that either decays spontaneously to elementary selenium and glutathione or is enzymatically converted under anaerobic conditions to hydrogen selenide (H₂Se) (Hsieh and Ganther, 1975). This central selenide pool serves either as the basis for methylated derivatives that are excreted or as a donor for conversion into hydrogen selenide, which is the common precursor for further metabolism into Se-cysteine (Ganther, 1966; Mozier et al., 1988; Ip et al., 1991; Berry et al., 1993; Guimaraes et al., 1996). In contrast to Se-cysteine, mammalian organisms are unable to synthesize Se-methionine (Levander and Burk, 1986). Conversely, Se-methionine uses the trans-sulfuration pathway of the sulfur amino acids and thus can be converted into Se-cyst(e)ine (Beilstein and Whanger, 1992).

The toxicity of selenium is known for a long time, and the acute toxicity of organic and inorganic resorbed selenium compounds has an LD₅₀ in the range of 2–5 mg kg⁻¹ (Combs and Combs, 1986).

SELENIUM CARCINOSTATIC TOXICITY

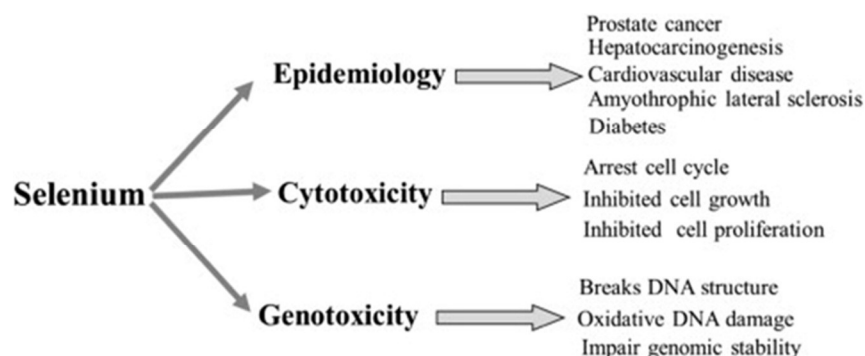
As an essential nutrient, Se affects the functions of several specific intracellular selenoproteins as an essential constituent of selenocysteine (Se-Cys).

Epidemiological studies indicate that Se deficiency can induce several diseases in humans. Se plays a vital role as an antioxidant in humans. Considering its importance for humans, the recommended dietary intake for Se is 55 and 30 µg day⁻¹ for healthy adults in the US and Europe and 50–250 µg day⁻¹ for adults in China by Chinese Nutrition Society (Sun et al., 2014).

The anticarcinogenic nature of Se has been investigated for several decades. However, researchers found that there is an inverse relationship between Se content and cancer risk. For example, Whanger (2004) reported that Se doses at 100–200 µg day⁻¹ inhibit genetic damage and cancer development in humans; however, at ≥400 µg day⁻¹, Se probably induces cancer (Zeng and Combs, 2008). Although excessive Se can induce cancer in humans, the relation between Se and cancer is still unclear.

Figure 1 shows high Se can induce carcinogenesis, cytotoxicity and genotoxicity.

Figure 1: Selenium toxicity in humans and rats



Source: Selvaraj (2012), Selvaraj et al. (2013)

CONCLUSION

It seems that recognition of selenium compounds that produce superoxide and hydrogen peroxide, fully

accounts for the toxicity and carcinostatic/cytotoxic activity of selenium compounds. Also, results reveal selenium carcinostatic activity normally occurs only at dietary levels that approach systemic selenium toxicity.

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