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SELENIUM IN THE ENVIRONMENT: ESSENTIAL OR TOXIC TO HUMAN HEALTH?

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Abstract

Selenium (Se) is a mineral of fundamental importance for human health. Se status in general population is very important due to its remarkable benefits to the human body: antioxidant, hormonal regulator, anti-carcinogen. At the same time Se can be toxic leaving a narrow optimal range for optimal intake. Both excess and deficit are known to cause a wide range of clinical manifestations. Even though a large body of evidence provides vast information about Se, the exact molecular mechanisms of its effect in physiologic and pathologic conditions remain unknown. The individual Se requirements are still in debate, as there is a marked difference in the distribution of serum selenium levels of individuals in the general population. The general opinion is that in the last 20 years the requirements were higher than the international dietary reference values for selenium. There are several issues related to environmental Se and human health: the link between Se status in soil-plants-human body (plants extract Se from soil incidentally and the type of soil influences the Se content in food), necessity of Se supplementation in general population, therapeutic effects of Se in various diseases. The lack of suitable frameworks in general population represents an issue for the assessment of health/economic impact of Se deficiency. Further researches are needed in: agriculture, economics and health in order to determine the costs/benefits relationship and monitor the health outcomes of Se supplementation.

Key words: agriculture, environment, health, selenium, selenoenzymes

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1. Introduction

Selenium (Se₇₉³⁴) was first isolated in 1817 by Jacob Berzelius but its importance in human health and ecosystem was recognized in 1957. The name is derived from Selene, the Greek goddess of the moon and is a nonmetal of the same family as sulfur and oxygen (Mehdi et al., 2013). Se is present in the environment (water, soil and air) in very low concentrations (< 1µg/g). The natural environment has a profound influence on the Se content of soil, crops and human tissues. Se is indispensable for

normal plant growth and functioning of animal organisms (Bem, 1981). Se from soil and water enters the food chain through the root ways of plants and aquatic organisms (Saranac et al., 2011). Se is an essential element for human health. Food as source of Se in human nutrition can contain inorganic (selenite, selenate) or organic (Se-amino acids, Se-methylated and Se-proteins) forms of Se. The organic forms are more available than the inorganic ones (Ježek et al., 2012). The body pool of Se is: 30% in the liver, 15% in the kidney, 30% in the muscle and 10% in the plasma. Most of Se in tissues and fluids (blood) is

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found in proteins (seleno-proteins, selenotrisulphides and other acid-labile Se compounds) (FOA/WHO, 2001).

While moderate Se deficiency has no or subtle clinical symptoms, severe Se deficiency leads to: Keshan disease, characterized by failure of myocardium function (cardiomyopathy) and Kashin-Beck disease, characterized by osteoarthropathy (damage of cartilages causing deformations of bone structures) (Ježek et al., 2012). Low Se supply is linked to the incidence of prostate cancer; also growth retardation, impaired bone metabolism and osteopenia were found in Se-deficient male rats. Se deficiency was associated with cardiovascular diseases, thrombosis and atherosclerosis (Kohrle et al., 2005). The toxic effect appears when chronically over limit daily intake of Se is present (Ježek et al., 2012). In seleniferous areas it is possible that people consuming locally grown food may manifest signs of Se toxicity (selenosis).

The environmental conditions and agricultural practices have a great influence on Se content in different foods. The Se load in vegetables, wild-grown mushrooms fruits, meat, fish and water depends on factors such as: soil composition, agricultural practices, plant species, and pollution. Therefore, the average adult Se intake can vary by geographic area and others multiple variables. China, India, Middle-East and some European countries are extremely low in soil Se resulting in Se deficiency in the local population (Dharmasena, 2014). In contrast, soil from driest regions tends to concentrate high quantities of Se. Also, alkaline soils release more Se than acid ones (Joy et al., 2015).

The safe level of total Se intake for an 70 kg adult who subsists on a normal diet (reference dose-RfD) has been set at 350 µg/day corresponding to 5 µg Se/kg body weight/day (Dharmasena, 2014). The role of Se is very important in living organisms. The understanding the Se soil-plant-animal axis is mandatory in covering the requirement of the organisms in this element (Mehdi et al., 2013).

There are many issues related to environmental Se and human health, in terms of the link between soil-plants-human body and Se, need for Se supplementation in general population in order to prevent severe deficiency but also to avoid Se excess or toxicity. The lack of suitable frameworks in general population represents an issue for the assessment of health/economic impact of Se deficiency. This article reviews the role of Se in human health in close relation with its cycle in nature (soil-water-plants) emphasizing the necessity of assessing Se concentration in human body in order to establish the right amount of Se supplementation.

2. Selenium in nature

2.1. Physiochemical characteristics

Se is a nonmetal mineral, a trace element and an essential micronutrient (Winther et al., 2014). Six Se isotopes coexist in nature (mass number: 74, 76,

77, 78, 80 and 82). At ordinary temperature Se is a solid substance. Se occurs naturally in inorganic forms: selenite (SeO_3^{2-}), selenide (Se^{2-}), selenate (SeO_4^{2-}) and selenium element and organic forms: selenomethionine and selenocysteine. The inorganic, anionic forms are highly soluble, mobile, bioavailable and potentially toxic. The organic forms come from decomposition of plants that accumulate Se (Mehdi et al., 2013).

2.2. Selenium in soil

The basic source of dietary Se for humans and animals is soil. Soils are the major source of Se for plants, soil Se existing in various forms: elemental Se, selenates, selenides and organic Se compounds. Different geographic locations have different Se content. Se availability for plants is decreased by low pH and high concentrations of sulfur and phosphorus (Hall et al., 2013). Se tends to be concentrated in the soil of the driest regions in the world. The toxic effect on animals occurs in these regions. Alkaline soils release more Se than acid ones (Mehdi et al., 2013). Soil with Se content lower than 0.3 mg/kg-1 is insufficient and higher than 3 mg/kg-1 is toxic. The average Se content varies with the soil type, climate and area (Ježek et al., 2012). The chemical form of Se in the soil is determined by soil pH and redox potential: Se binds to iron oxide clay minerals and organic material. Forest soils efficiently retain Se and then incorporate it into low-molecular-weight fractions of humic substance (FAO/WHO, 2001; Statescu and Cotiusca-Zauca, 2006).

Soil type may influence the selenium content of food crops. Use of soil-specific composition data can improve estimates of dietary mineral supplies. In some countries such as Malawi total Se concentrations in maize grain from calcareous soils was greater than in grain from non-calcareous soils (Joy et al., 2015).

2.3. Selenium in water

Aqueous Se can exist in three oxidation states: selenide, selenite and selenate in natural waters. The dominant hydrolysis complexes for selenide, selenite and selenate are: HSe^- , HSeO_3^- and SeO_4^{2-} , respectively, in the pH range of 3 to 9. Porcella (1991) quoted by Parkman and Hultberg (2002) described the biological pathways by which Se is transported in freshwater systems (Fig. 1). The major entries into the food web are: incorporation of Se by phytoplankton and microheterotrophs and uptake from sediments by benthic organisms. Both these two pathways may transform Se to new forms or pass it to higher trophic levels by being eaten (Parkman and Hultberg, 2002).

Se compounds toxicity to aquatic organisms is a very important issue. Se-methionine is extremely toxic to Daphnia at concentrations of 4 to 8g/l-1 while lethal concentrations for midge larvae were about 1000 times higher. Se at the same concentrations in mixtures of sea water and

seleniferous leachate from coal fly-ash was less toxic than the pure sodium selenite.

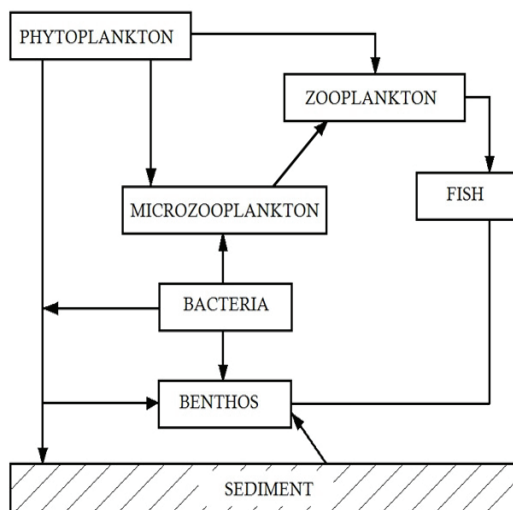


Fig. 1. Potential C and Se pathways in a model freshwater ecosystem (Porcella et al., 1991 cited by Parkman and Hultberg, 2002)

There are different models to determine the transport in water and sediments (Pintilie et al., 2007) and also the uptake kinetics, toxic effects on growth, reproduction and mortality of various chemical forms of Se to multiple aquatic organisms. The fish may be considered as sensitive as lower organisms for certain Se-exposure. The most important aspect of Se in aquatic organisms is not the direct toxicity to the organisms themselves, but the position in the food chain and the dietary source of the Se they provide to organisms that feed on them (Parkman and Hultberg, 2002).

2.4. Selenium in plants

The role of Se in the life cycle of plants which absorb organoselenium compounds accumulated in the soils of semiarid areas is very important (Revanasiddappa and Kumar, 2001). Se concentration in plants is in direct relation with its surrounding soil content. There are seleniferous plants, Se accumulating plants and others plants with an average content of Se (Mehdi et al., 2013).

Uptake of Se by plants is influenced not only by the Se content in soil, but also by the Se form, soil reaction, soil redox potential, mineral structure of soil, mineral fertilizers, atmosphere and rain precipitation (Fig. 2). According to the amount of Se accumulated, plants can be grouped in three categories:

- Selenium non-accumulators containing up to 25 mg Se/kg⁻¹ of dry matter (cereals, potatoes, grass, vegetable).
- Secondary selenium accumulators absorb from 25 up to 100 mg Se/kg⁻¹ (various species as Aster, Astragalus, Atriplex).
- Selenium accumulators can contain 100-10000 mg Se/kg⁻¹ of dry matter (various species as Stanleya, Haplopappus) (Ježek et al., 2012).

Transformation and assimilation of Se in plants is in relation with sulfur metabolism. Most plants take up selenite because of its similarity to sulfate and metabolize it via the sulfur assimilation pathway (Mehdawi et al., 2011). The toxic effect of Se in plants is attributed to interactions with sulfur metabolism. Replacement of sulfur cysteine and methionine amino acids with selenium amino acids can disturb the biochemical reactions and enzymatic functions within the cells (Ježek et al., 2012).

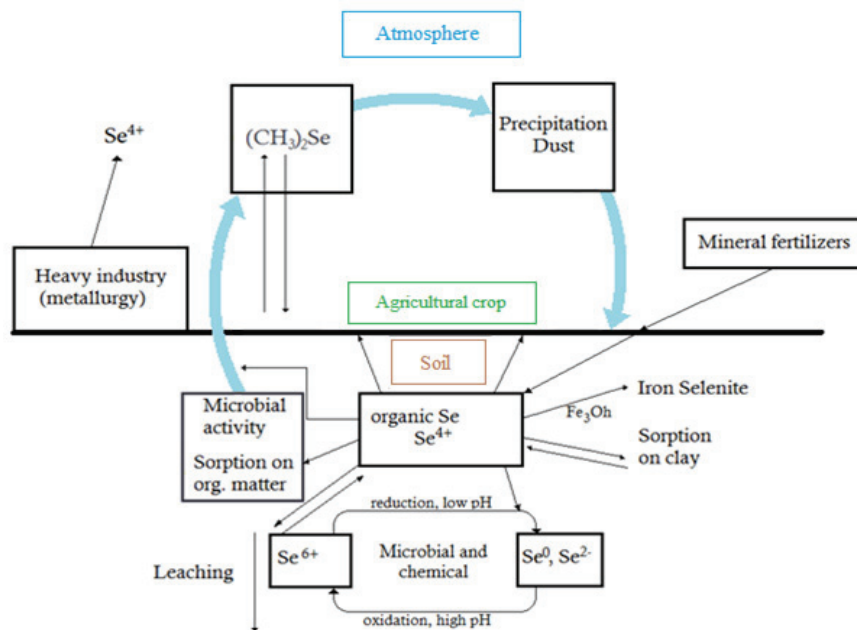


Fig. 2. Selenium cycle in an agroecosystem (Gissel-Nielsen, 1998, cited by Ježek et al., 2012)

3. Selenium and health

3.1. Selenium metabolism

Se enters the food chain through plants and the amount of Se in food is directly correlated with the level of Se in soil (Li et al., 2014). In animals the absorption of Se takes place in the duodenum and caecum. Inorganic forms are absorbed by simple diffusion or by active transport through a sodium pump. Organic forms (selenomethionine, selenocysteine) are absorbed in the small intestine by an active mechanism. The hepatic Se concentration reflects the level of intestinal absorption. Se is transported by blood in form of selenoprotein P. Urine is the dominant route of excretion of Se in animals (Mehdi et al., 2013). From food 70-95% of organic forms are absorbed, than metabolized as proteins. The inorganic forms are absorbed and deposited in tissues in small extent (Ježek et al., 2012). In the human body Se has different concentrations in different organs: 30% in the liver, 15% in the kidney, 30% in the muscle and 10% in the plasma. Most of the Se in tissues is found in proteins (seleno-proteins, selenotrisulphides and other acid-labile Se compounds) (FOA/WHO).

3.2. Selenium and nutrition

Different types of food, such as biological materials and dairy products are important sources of Se in human diet (Shaltout et al., 2011). Serum Se levels are influenced by the dietary Se concentrations, which in turn are dependent on the soil Se content, form and distribution of Se in foods (Se from plant source foods is more bioavailable than animal source foods) (Lander et al., 2008).

The recommended Se daily intake in adulthood varies greatly according to different

authors, countries and organizations (Table 1). Schrauzer and White (Dharmasena, 2014) estimated that daily Se intake per person is in the range of 90-168 µg. In Asia, Africa and many European countries the daily Se intake is under the recommended dose. Se deficiency has negative consequences mostly in seniors, pregnant and lactating women, growing and developing children (Ježek et al., 2012), thus for different life stages there are different dietary allowances (Table 2). In order to provide a safe total Se intake the reference dose (RfD) from all nutritional sources for a 70 kg adult has been set at 350 µg/day, corresponding to 5 µg Se/kg body weight/day (Dharmasena, 2014).

There are different ways to increase the dietary Se intake: increased consumption of foods rich in Se (meat, fish or grains), nutritional educational programs, water Se supplementation, pharmacological substances, Se fortification of food and bio fortification (Lopez-Bellido Garrido and Lopez Bellido, 2013). It is necessary to adopt agricultural-based programs to enhance the mineral composition of food in regions with risk of Se deficiency by enriching fertilizers with Se (Yan et al., 2010, Chilimba et al., 2011). In 1984, in order to improve Se content in food, Finland implemented the Se-enriched fertilizers (agronomic biofortification) which have continued to date. All types of cereal grains and all grain fractions are enriched with Se when Se forms are added to fertilizers (Hurst et al., 2013). Se supplementation of fertilizers has affected all domestic agricultural products. The mean Se intake of the population was calculated on the basis of food consumption statistics, urinary Se excretion data and average serum concentration of both urban and rural people. Enrichment of fertilizers with sodium selenite in areas with low Se seems to be an efficient way to increase Se concentration in food (Varo et al., 1988).

Table 1. Recommended daily intake in adults (men/women) for different countries and organizations, based on the minimum quantity necessary to optimize the GPX activity (WHO consider recommendable minimum intake to attend 2/3 from optimum activity of GPX) DRI (Dietary Reference Intake), RNI (Reference Nutrient Intake), PRI (Population Reference Intake), NRE (Normative Requirement Estimate) (Lopez-Bellido Garrido and Lopez Bellido, 2013, with permission)

<i>RDA (Recommended Dietary Allowance) µg Se per day</i>							
	<i>DRI/RDI</i> <i>USA</i>	<i>RNI/RDA_U</i> <i>K</i>	<i>PRI/RDA</i> <i>EU</i>	<i>NRE</i> <i>WHO</i>	<i>RDA</i> <i>USA</i>	<i>RNI/RDA</i> <i>WHO</i>	<i>RDI/RDA_{AUS}</i>
Country/ Organization	USA 1989 (Thomson, 2004)	UK 1991	EU 1993 (Thomson, 2004)	WHO 1996	USA 2000	WHO 2004	AUSTRALIA & NE 2005 (Hawkeford and Zhao, 2007)
Men	70	75	55	40	55	34	70
Women	55	60	55	30	55	26	60

Table 2. Maximum safe daily intake of Se for particular age categories (Ježek et al., 2012)

<i>Life stage</i>	<i>Age</i>	<i>Dose (µg Se.day⁻¹)</i>
Infants	0-6 months	45
	7-12 months	60
Children	1-3 years	90
	4-8 years	150
	9-13 years	280
Adults	>14 years	400

3.2.1. Role of selenium in the human body

Se is an essential micronutrient important for many aspects of human health (Verma et al., 2011) which plays a major part in optimal endocrine response, immunomodulation and inflammatory process (Dharmasena, 2014). Se is incorporated into cysteine forming the 21st amino acid used during protein synthesis. Selenoproteins have vital functions in the body: essential antioxidant enzymes that fight cancer, regulators of thyroid function, structural proteins in sperm required for fertility, reduce virulence associated with certain viral infections (Weeks and Hanna, 2012).

The effect of Se in humans is concentration-dependent, ranging from an antioxidant activity in the nanomolar-micromolar range to a potentially prooxidant activity at concentrations higher than required for selenoprotein synthesis (Negro, 2008). There are two distinct families of Se-containing enzymes: glutathione peroxidases and thioredoxin reductase involved in controlling tissue concentrations of oxygen-containing metabolites and iodothyronine deiodinases which are essential in the conversion of thyroid hormone thyroxine to its active form- triiodothyronine (FAO/WHO, 2001).

The selenoenzymes are capable of modifying cell function by acting as antioxidants and the redox status; also they influence cell growth, apoptosis, and modify the action of cell signaling systems and transcription factors. Se is incorporated co-translationally into the selenoproteins as a selenocysteine residue that is fully ionized at physiological pH and acts as a very efficient catalyst. Most of known selenoproteins are expressed in the thyroid gland: glutathione peroxidases (GPXs), thioredoxin reductase (TRs) and iodothyronine deiodinase (type D1, D2 and D3). Selenoprotein P,

W, selenophosphate synthetase and many others exist in different organs and have multiple actions, many of them unknown (Beckett and Arthur, 2005) (Table 3).

The testis contains high concentrations of Se and experiments on selenoprotein P-knockout mice indicate that Se is essential in testicular function. GPX4 provides the link between Se, sperm and male fertility (Beckett and Arthur, 2005). Se has insulin-mimetic properties: an insulin-like effect of Se in cultured rat adipocytes include stimulating glucose transport, phosphodiesterase activity and ribosomal phosphorylation (Beckett and Arthur, 2005). The beneficial effect of Se on autoimmune mechanism is a complex one in which the inhibitory effect on HLA-DR molecule expression and anti-oxidative capacity are involved (Balázs and Kaczur, 2012). The thyroid contains more Se per gram of tissue than any other organ (Efthymidis and Wiersinga, 2014).

Adequate Se intake assures thyroid hormone synthesis and metabolism and also protects the gland from damage from excessive iodine exposure. In regions with both deficit in Se and iodine it is mandatory to normalize Se intake before iodine supplementation to prevent endemic goiter (Saranac et al., 2011).

3.2.2. Selenium deficiency

Se deficiency can affect human health in different ways. The severe endemic deficiency is associated with: Keshan disease (congestive cardiomyopathy), Kaschin-Beck disease (chronic, endemic osteochondropathy) and the mild one with limited expression of various Se-dependent enzymes (Lopez-Bellido Garrido and Lopez Bellido, 2013). Causes of deficiency are low dietary intake or poor intestinal absorption.

Table 3. Mammalian selenoproteins and their function (Beckett and Arthur, 2005)

<i>Selenoproteins</i>	<i>Proposed Function</i>
Glutathione peroxidase (GPXs)	
GPX1	Antioxidant in cell cytosol; Se store?
GPX2	Antioxidant in gastrointestinal tract
GPX3	Antioxidant in extracellular space and plasma
GPX4	Membrane antioxidant; structural protein in sperm; apoptosis?
GPX5	Unknown
GPX6	GPX1 homologue?
Thioredoxin reductase (TRs)	Multiple roles including dithiol-disulphide oxoreductase Detoxifies peroxides, reduces thioredoxin (control of cell growth); maintains redox state of transcription factors
TR1	Mainly cytosolic, ubiquitous
TR2	Expressed by testes
TR3	Mitochondrial, ubiquitous
Iodothyronine deiodinases	
Type D1 and D2	Converts thyroxine (T4) to bioactive 3,5,3'-tri-iodothyronine (T3)
Type D1 and D3	Converts thyroxine (T4) to bioinactive 3',3',5' reverse T3
Selenoprotein P	Selenium-transport protein. Antioxidant on endothelium
Selenoprotein W	Antioxidant in cardiac and skeletal muscle?
Selenophosphate synthetase (SPS2)	Synthesis of selenophosphate for selenoprotein synthesis
15 kDa Selenoprotein (Sep 15)	Protects against cancer?
H, I, K, M, N, O, R, S, T, V	Role largely unknown

The non-endemic form is more common in individuals maintained on parenteral or enteral feeding for long periods of time. In infants Se deficiency may be present when formulas with low Se content or without added Se are used. Clinical manifestations are very uncommon and nonspecific: myalgia, muscular weakness, congestive heart failure. In order to develop such conditions the daily Se intake must be under 10 μg per day. The endemic forms Keshan disease and Kashin-Beck disease present variable distribution depending on geochemical factors. Acid soils high in organic matter and iron oxide content may be responsible for fixing Se in forms which are poorly absorbed by staple crops (FAO/WHO, 2001).

The clinical features of Keshan disease are acute or chronic episode of a heart disease characterized by cardiogenic shock, enlarged heart, congestive heart failure, cardiac arrhythmias and ECG changes. There are 4 types of clinical manifestations: acute, chronic, subacute and insidious. During autopsy, moderate enlargement with dilation of all heart chambers was found in most cases. Histopathologically, multifocal necrosis and fibrous replacement of myocardium are scattered throughout the heart muscle (Chen, 2012).

Kashin-Beck disease is an endemic osteochondropathy. The disease starts in childhood and affects the growth of joint cartilage, the joints become deformed and painful, and the worst forms result in dwarfism. The joints most frequently involved are: finger, wrist, ankles, knees and elbows. Geographically Kashin-Beck disease has a typical endemic distribution in Eastern Siberia of Russia, China and North Korea. Three major environmental hypotheses including endemic selenium deficiency, cereal contamination by mycotoxin-producing fungi and high humic acid levels in drinking water have been proposed (Farooq et al., 2012).

3.2.3. Selenium toxicity

Se is a complex element due to its properties of being both essential and toxic, leaving a narrow range within which intake is healthy. Organic and inorganic forms of Se have similar toxic effects. Selenosis is the most common disease as is due to over limit intake of Se from food. The clinical signs

are: abnormalities of nervous system, fragility and loss of hair and nails, nausea, mottled teeth, hives, diarrhea (Ježek et al., 2012, Nazemi et al., 2012). In humans, at higher levels, Se becomes toxic and nonspecific replacement of cysteine by selenocystine in protein disrupts protein function causing toxicity and death (El Mehdawi et al., 2011).

The upper limit in relation with the toxic effect varies with the geographic region and population characteristic. In some US regions with naturally high Se content in soil, a daily intake of 724 μg per day has no toxic effects. In China selenosis occurs when the daily Se intake is over 910 μg per day. Moreover, when daily Se doses of 1600-3200 μg were used in order to treat cancer only mild symptoms of toxicity were present (Ježek et al., 2012). Exposure to air pollution can lead to Se excess causing brain damage in young people and Se increase in frontal lobe with age in exposed subjects (Calderón-Garcidueñas et al., 2013).

The signs and symptoms of human overexposure to Se are not well defined. Common clinical features are: icteric skin, gastrointestinal disturbances, hair loss and nail dystrophy when food supply exceeds 900 $\mu\text{g/day}$. There are no sensitive biochemical markers for Se intoxication. In their absence it is suggested that the tolerable upper intake level for Se should be 400 $\mu\text{g/day}$ for adults (FOA/WHO, 2001). The recommended daily intake, tolerable upper nutrient intake level, insufficient and toxic intake for Se are shown in Fig. 3.

3.2.4. Selenium supplementation in thyroid disorders

The role of Se supplementation is still debated even though there are in vitro and in vivo data on its positive effect in reducing cancer-associated mortality, severity of autoimmune disease, oxidative damage and improving mental health, reproductive performances, evolution of AIDS (Weeks and Hanna, 2012). Autoimmune thyroid diseases arise due to complex interactions between environmental and genetic factors. Low birth weight, iodine and selenium excess or deficiency, reproductive span, parity, stress, seasonal variation, radiation, smoking, allergy, viral and bacterial infections have an important role in the development of thyroid autoimmune disorders (Prummel et al., 2004).

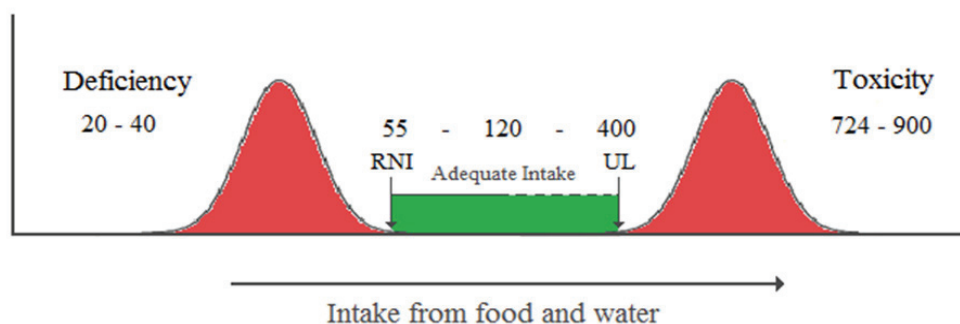


Fig. 3. Distribution and requirements to prevent Se deficiency and toxicity (the values are in μg Se per day; RNI= recommended nutrient intake, UL= upper limit)

The thyroid is the endocrine gland with the highest Se content because it expresses specific selenoproteins. Se status appears to have an important impact on thyroid metabolism (selenoproteins have a major role in the synthesis and action of thyroid hormones) and thereby seems to be involved in thyroid pathology (Balázs and Rácz, 2013; Bhuyan et al., 2012). In a recent cross-sectional, prospective European study (Krassas et al., 2014) a linear correlation of Se levels and Se protein P was found in patients with thyroid disorders, indicating a less than optimal Se status. Patients with Graves' disease and Hashimoto thyroiditis had significantly lower Se levels compared with patients with non-autoimmune disease. The lower levels of Se in patients with autoimmune thyroid disorders suggest that Se supplementation may be useful. The effect of Se supplementation in autoimmune thyroid disorders is controversial however the European Food Safety Authority (EFSA, 2009) advise for a normal thyroid function a daily dose of 200 µg/day with a maximum recommended dose of 350 µg/day.

Combination of myo-inositol and Se improves the subclinical hypothyroidism in autoimmune thyroiditis (Nordio and Pajalich, 2013). Se (selenomethionine 200µg per day) and l-thyroxin therapy is effective in decreasing anti-thyroid peroxidase antibodies in patients with autoimmune thyroiditis (Duntas et al., 2003). Se 200µg per day for 9 months is effective in increasing GPx activity and decreasing thyroid autoantibody levels (Turker et al., 2006). In children with autoimmune thyroiditis, 100-200 µg sodium selenite per day does not decrease thyroid autoantibody levels (Bonfig et al., 2010). Se supplementation could alleviate inflammatory thyroid lesions by inhibiting IL-2 expression and others cytokines (Tan et al., 2013). Treatment with 200µg selenium-enriched yeast for 12 months in autoimmune thyroiditis was used to assess the quality of life (Winther et al., 2014).

Although clinical applications still need to be defined, in pregnant women with Hashimoto thyroiditis Se supplementation significantly decreases the rate of postpartum thyroiditis and hypothyroidism (Drutel et al., 2013). Also, the beneficial effect of Se on mild Graves's inflammatory orbitopathy is being studied (Dharmasena, 2014). A Cochrane systematic review (van Zuuren et al., 2013 cited by Effraimidis and Wiersinga, 2014) concluded that present data do not allow confident decision making about the use of selenium supplementation for Hashimoto's thyroiditis. Further studies are needed to support the beneficial effect of Se in thyroid disorders.

3.2.5. The "protective" effect of Se against methylmercury (MeHg) exposure

For many years Se was considered as a „natural" Hg antagonist that counteracts symptoms of toxicity related to high Hg exposure. The interactions between Se and Hg are important for the

understanding of the environmental behavior and toxicological effects of these two elements. This is the subject of interdisciplinary research which involves: geology, medicine and other disciplines.

The antagonistic effect of Se on the toxicity of Hg in mammals and aquatic organisms is very complex and still in debate in terms of mechanism that explain the protective effect of Se compounds on mercuric mercury (Hg^{2+}) and methylmercury (CH_3Hg^+) toxicity.

Animal studies have indicated that the toxic effects of MeHg increase with decreasing Se intake. In brain, the toxic effect is directly correlated to the Hg-to-Se molar ratio and is dramatically increased when this ratio is greater than 1:1 (Brockman, 2011 cited by Zhang, 2014).

Also, others authors suggest that the protective effect of selenite on the toxicity of Hg^{2+} in mammals is determined by in vivo formation of mercuric selenide (HgSe), a stable and biologically inert complex (Zhan, 2014). The most recent proposed mechanism explains the toxicity of Hg by the restricted synthesis and activity of selenoenzymes (Ralston and Raymond, 2010).

In humans maternal exposure to MeHg during pregnancy is directly correlated with later fetal neurodevelopment. Based on this conventional assumption, epidemiological studies were performed in order to assess the adverse effects of maternal exposure to MeHg on fetal development, but the results of these studies are contradictory (Zhan, 2014).

In fact, it is possible that the toxicity of MeHg is not correlated with maternal exposure to MeHg but with a relative deficiency in Se (Khan and Wang, 2009 cited by Zhang, 2014). The observed toxicity of Hg is at least partially attributable to Se deficiency caused by Se-Hg complexation (Khan and Wang, 2009; Watanabe et al., 1999 cited by Zhang, 2014).

3.3. Pitfalls in the assessment of Se in the environment and humans

The determination of Se is of considerable interest because of its contrasting biological effects: toxic element as well as a trace element for animals and humans. Sampling of biological material for Se determination is not difficult (care must be taken only that sample to be representative), for water sampling only filtration and concentration are necessary due to the low Se content. Air sampling is much more difficult due to the volatility of its compounds. Sample decompositions procedures for Se determination are various: instrumental nuclear activation analysis (INAA), atomic absorption spectrometry (AAS), electrothermal atomic absorption spectrometry (ET AAS), hydride generation atomic absorption spectrometry (HG AAS), fluorimetry, X-ray fluorescence analysis (XFA), and gas-liquid chromatography (GCL) (Bem, 1981) but a high care is needed for selection of a

proper analytical procedure for determination of Se in foods and biological material because of biased results produced (Falandysz, 2013). Chromogenic reagents used for Se determination by various spectrophotometric methods are: dithiozone, chromotropic acid, J-acid, Variamine Blu (Revanasiddappa and Kumar, 2001).

Se content in human hair is a useful indicator for human Se intake and status (Li et al., 2014) and so are measurements in plasma, serum or in such tissues as kidney and liver. An indirect method to assess Se is the measurement of GPx activity in erythrocytes.

4. Conclusions

Se is essential to humans playing an important role as antioxidant, regulator of thyroid function and many others organs as component of structural proteins. Se can be considered a required dietary nutrient but the right amount for different populations it is still in debate. This important nutrient for human health can become a real menace when a certain dosage is exceeded. If severe diseases are directly related to Se insufficiency, Se excess can lead to severe illnesses.

The importance of environmental elements: pollution, precipitations, fertilizers, soil type on Se supply, absorption and excretion makes more complicated the issue on optimal intake. There are many problems to solve: normal Se concentration in human body, optimal intake and therapeutic effect of pharmacological doses of this micronutrient in various diseases.

Researchers in various scientific fields have to collaborate in order to develop new methods and technologies able to provide solutions and answers to these complex problems.

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