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Selenium in Soil-Crop-Animal System: A Holistic Perspective to Manage Animal and Human Health

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Abstract: Selenium (Se) dependent enzymes play important roles in physiological functions such as thyroid hormone metabolism, strengthens anti-oxidant defense system and immune system. However, about 800 million people worldwide are believed to be deficient in Se which is attributed to low Se levels in the soil. This is because Se in plant and animal products in human diet depends upon the available Se in the soil. Deficiency of Se can be prevented or treated by adequate dietary intake or through direct supplementation. There have been reports that patients with dilated cardiomyopathy, HIV viral loads and cancer have responded to Se supplementation. However, food fortification has been found to be more efficient than supplementation. Both agronomic biofortification and genetic biofortification have been used to increase Se content of food crops and animal products. Genetic engineering makes use of key genes of Se hyperaccumulators to increase Se accumulating potential of food crops. Agronomic biofortification increases Se content of food crops by adding Se rich fertilizers to the soil or foliar application of Se. Selenium can also be added to animal diets or feedstuff to increase Se content of meat, eggs, and milk. Although inorganic forms of Se are approved as feed additives, they are less efficient than organic sources such as selenomethionine (SeMet) which is the dominant form in plants and animals. Animal products have been found to have higher Se content than plant products with fish having the highest Se content. Fruits and vegetables have a low content of Se probably because of their low protein content. Recommendations for dietary intake of Se vary with country, age and sex. There are concerns that the present recommended Se daily allowance may not be adequate due to discovery of other selenoenzymes with higher Se requirements than gluthathione peroxidase. There may be a need to review the current recommended daily allowance for Se in order to improve human health.

Keywords: Selenium, Supplementation, Dietary Intake, Fortification, Selenomethionine

1. Introduction

Selenium is an essential nutrient for animals and human but not yet established as an essential nutrient for plants. However, Se has many beneficial effects on plant growth such as growth promoting effect, anti-oxidative effects, senescence delay, and reduced herbivory [1]. Selenium plays a role in many important physiological functions in human and animal health because it's a component of selenoproteins such as glutathione peroxidase, thioredoxin reductase, and thyroid hormone deiodinase families [2]. These Se dependent enzymes play a wide range of biological functions involving thyroid hormone metabolism, the body's antioxidant defense systems, the adaptive and acquired immune system and prevention of certain cancers [3]. In addition, selenoproteins such as glutathione peroxidase and thioredoxin reductase play an important role in maintaining bone homeostasis and protecting against bone loss [4]. Selenium has also been shown to play an important role in the normal functioning of the cardiovascular system even though many studies remain

inconclusive [3].

Various diseases have been linked with deficiency of Se in both animals and humans. Low dietary intake of Se may cause a number of health problems such as heart diseases, hypothyroidism, reduced male fertility, weakened immune system and enhanced susceptibility to infections and cancer in the human population [5, 6]. Selenium deficiency is revealed in symptoms such as muscular dystrophy and pain, inflammation of the muscles, fragile red blood cells, necrotic liver degeneration, hair or skin abnormal coloration and exudative diathesis in many warm-blooded animals [7, 8]. However, there is a thin line between Se deficiency and toxicity with high concentrations being toxic [9].

Low Se levels in humans and animals have been associated with low Se levels in the soil because the soil is a source of Se for crops and forages consumed by animals and humans [10]. There are geographic variations in soil Se concentrations around the world, ranging from high concentrations in soils of the USA and Venezuela to low concentrations in Korea, some regions of China and some parts of Europe [11, 12]. Wide differences in geology, soil, climatic factors, foods and fodder from various parts of the world imply a high variability in their ability to provide selenium for dietary intake [13, 14].Many parts of the world such as Europe and Asia are characterized by Se deficiency in soils, crops, animals and humans. About 800 million people worldwide are believed to be deficient in Se [15]. In order to correct the deficiencies and meet the Se daily intake requirements, both animal and human diets are supplemented either directly or via biofortification of forage, animal feed, food crops and food products. Selenium is supplemented through application of either inorganic or organic sources. Both genetic and agronomical fortification can also be used to increase Se levels in food crop and forage to ensure that Se requirements are met. Selenium is introduced into the food chain via the soil-crop-animal system to increase the daily intake and meet the requirements for both animal and human health.

It is important to understand the origin and impact of Se deficiencies in living systems in order to correct the deficiencies and ensure adequate nutrition of animals and human population for optimum health. Most of the past reviews on Se are on human health and geochemistry. Few have been able to discuss the effect of the soil-crop-animal system on both animal and human health. The goal of this review is to present a holistic soil-plant-animal system of sustaining animal and human health. This review elaborates on Se in the soil-crop-animal system; it explains supplementation in the livestock industry and supplementation for human health. It also discusses the methods of supplementation, assessment of Se status in tissues, intake recommendations for selenium and types of fortification to correct or prevent Se deficiency in animals and human populations.

2. Selenium Supplementation in the Livestock Industry

2.1. Selenium in the Food Chain

Selenium in food chain largely influences the selenium nutritional status of humans and animals. Animals predominantly live on plants or plant-based manufactured feeds, whereas human diets include both plant-based foods and animal products (meat, milk, and egg). The Se content of plants is directly affected by plant bioavailable Se levels in the soil in which they are grown, whereas the Se content of animal products (meat, milk, and egg) is determined by the Se levels in the plant-based diets consumed by the animals [15, 16]. Thus, the ultimate source of Se in the animal and human food chain is plant available soil selenium. Plants take up Se from the soil in the form of selenite or selenate and synthesize selenoamino acids with selenomethionine (SeMet) as the primary compound [17]. In plants, SeMet represents more than 50% of the total Se [18]; the other seleno-compounds in plants include Se-methylselenomethionine, selenocysteine and Se-methylselenocysteine [19]. So, biotransformation of inorganic Se to selenoaminoacids is a crucial physiological process for the entry of Se in the food chain. Since the Se content of plants depend on plant available Se in soil, the level of this element in human foods and animal feed varies in different parts of the world. Over half the world's population (over 3 billion people), mostly women, infants and children in the resource-poor families in the global South, suffer from severe malnutrition of Se and other micronutrients, Fe, Zn, I, etc [20, 21] primarily due to their deficiency in the soils [22]. Likewise, Se deficiency in livestock (Figure 1) is prevalent in many areas of the world [23].

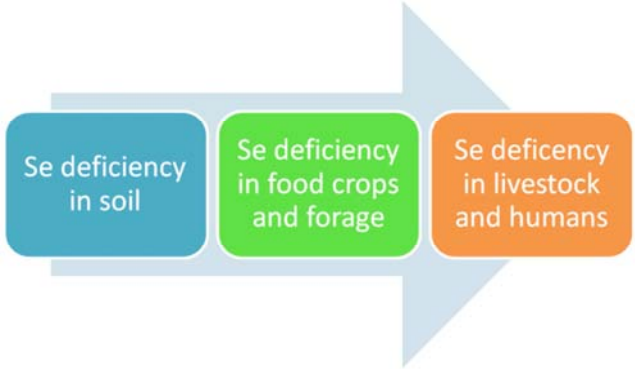

Figure 1. *Selenium deficiency.*

In contrast, there are places in various countries with seleniferous soils producing plants with toxic concentration of Se [24, 25]. Because agriculture is the primary source of Se for human and animal nutrition, the Se-deficient agricultural systems must be intervened with appropriate technologies to improving Se status of the food and feed systems that are failing to meet the Se nutritional needs of human and animal [26]. However, such agro-technological

interventions aimed at improving the Se status of food and feed crops should encompass a holistic food system perspective to assure that the interventions will be sustainable, and adopted by farmers and consumers [27].

2.2. Approval of Sodium Selenite and Sodium Selenate as Feed Additives by the US Food and Drug Administration

Feedstuffs (e.g., grains and forages) produced in many areas of the United States are either deficient or at least marginally deficient in Se for desired animal functions. Selenium intake in the diet can be increased by using Se rich feed ingredients or by providing selenized mineral supplements. Selenium deficiency diseases were widespread and severe in the 1960s. This alone caused huge economic losses annually to the livestock and poultry industry, which warranted an emergency fortification of feedstuff with selenium from a suitable source. Both sodium selenite and sodium selenate became promising candidates for this application because of a breakthrough discovery of the anti-necrotic activity of Se by [28]. Further studies revealed that these easily accessible inorganic selenium salts at effective dosage levels, unlike the previously tested organic selenium compounds, did not accumulate in organs and tissues to any significant extent. This meant that they could be used as feed additives without violating the "Delaney Clause", which is part of the "1958 Food Additives Amendment and Color Additives Amendments (section 409)" to the "1954 Federal Food, Drug and Cosmetic Act (FFDCA)" that prohibits the approval of an additive if it is found to induce cancer when ingested by people or animals, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in people or animals. However, it was not until 1974, when the U.S. Food and Drug Administration [29], after careful review of the available evidence, approved additions of sodium selenite and sodium selenite to feedstock setting up the initial maximum permissible levels (MPL) of selenium in the feeds.

The initially established MPLs were raised in the early 1980s.The current guidelines [30] for selenized mineral supplements are as follows: 1) manufactured premixes can contain Se up to 200 mg kg^{-1} and mineral supplements can contain Se up to 11.8 mg kg^{-1}, and 2) the total diet Se content should not exceed 0.3 mg kg^{-1} and total desired supplement is not over 3 mg $head^{-1}$ day^{-1}. This level can, however, be supplemented to diets regardless of the natural Se indigenous in the feedstuffs. The current regulation [30] allows the use of both sodium selenate and sodium selenite as mineral supplements in the feedstuffs. But because of its lower cost, sodium selenite is more commonly used. Sodium selenite is absorbed in the animal body passively via diffusion from the intestinal tract [31]. However, the inorganic Se supplementation (Figure 2) was found to be problematic in various ways.

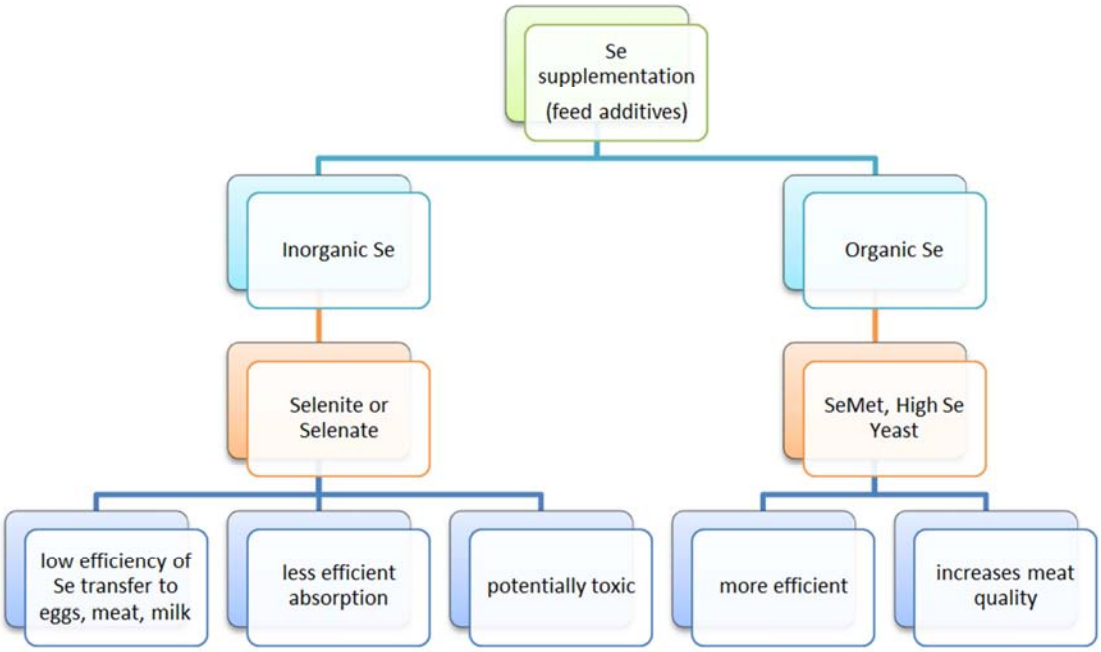

Figure 2. *Se Supplementation in Livestock.*

First, the absorption of sodium selenite is less efficient and occurs mainly by passive diffusion process [31, 32]. As a result, a greater proportion of consumed inorganic Se is simply excreted. Thus, supplementation in this form is unable to build and maintain Se reserves in the body. In addition, there is a low efficiency of Se transfer to milk, meat and egg. There are also concerns of potential toxicity via pro-oxidant activity, if the dietary supplementation is too high. Pro-oxidant activity is the antonym of antioxidant activity (the desired function of Se); sodium selenite and some other inorganic Se compounds such as Se dioxide and diselenides have such activity to catalyze the oxidation of thiols such as glutathione with a concomitant production of superoxide and other reactive oxygen species [33]. This catalytic reaction of

inorganic Se with thiols likely accounts for Se toxicity to cells in the major glutathione producing organs, such as the liver [33].

The pro-oxidant influence of sodium selenite in animals [33] is of particular concern when shelf life of the produced milk, meat and egg is considered [34, 35]. The pro-oxidant property of inorganic Se may also enhance multiplication of some pathogenic viruses. Sodium selenite can interact chemically with vitamin C (ascorbic acid) in the premix and the chemical reaction between them causes reduction of selenite to elemental Se (it often appears as pink particles in the premixes) and oxidation of vitamin C. The elemental Se is not absorbed in the digestive tract (hence it is excreted) and oxidized vitamin C is devoid of biological activity [36]. Therefore, nutritional benefits of both Se and vitamin C are lost. The reduction of selenite to elemental Se could happen in the premix/feed during storage or even in the digestive tract during digestion and absorption. Some other components in the premix like glucose monohydrate, corn starch or sucrose can reduce selenite to elemental Se in the same way [37].

2.3. Selenomethionine, the Chief Nutritional Form of Selenium

The majority of selenium in body tissues and fluids is present as either selenomethionine (SeMet), which is incorporated into general proteins and acts as a biological pool for selenium or selenocysteine (SeCys), which functions as an active center for selenoproteins [38]. It has been reported that irrespective of source, inorganic selenium must undergo a metabolic transformation prior to its assimilation into SeCys and ultimate incorporation into selenoproteins [39]. However, no such intermediate step is necessary for the incorporation of SeMet into general proteins.

Numerous authors [13, 31, 40-42] reported that in the regions with adequate plant bioavailable Se in soils, animals generally remain well-nourished with selenium just by consuming locally grown plant-based feeds which contain Se predominantly as protein-bound Se-Met. On the contrary, in the low Se regions, animals living predominantly on locally grown plant-based diets suffer from varying degree of Se-deficiency disorders. To combat Se-deficiency in the low Se regions, animals are often raised on feed fortified with sodium selenite; however, they still remain nutritionally deficient in Se to varying degrees, because these inorganic selenite and selenate supplements are not the natural nutritional form (which is indeed SeMet) of the element for the animals and the metabolic fate of inorganic Se differs substantially from that of SeMet.

Although, the rumen bacteria are able to produce some SeMet, the pertinent literature suggests that the amount of SeMet supplied from this source is indeed limited and does not meet the total needs of the animals [43]. As a result, supplementing SeMet produced measureable beneficial effects in both dairy and beef cattle industry. [44] reported that when dairy cows that were fed to Sel-Plex, a source of organic nutritional selenium primarily in the form of SeMet, they produced milk with a substantially higher selenium content and with a lower somatic cell count than the milk of control animals receiving the same amount of selenium as sodium selenite. Feeding Sel-Plex also increased the selenium content of blood, skeletal muscles, and in colostrum of calving cows. The Se-rich colostrum is highly beneficial to the immunity and survival of the calves. As SeMet is also naturally present in animal muscles [45], supplementation with SeMet increases meat quality as well, providing the basis for the commercial production of Se-rich meat that would improve human Se-nutrition [43]. In poultry, when feed contained SeMet, the layers produced eggs with a substantially higher SeMet content [46]. The other studies provided unequivocal evidence that humans retain substantially more Se in their organs and tissues when they obtain this micronutrient in the form of SeMet than from sodium selenite or selenate.

2.4. High Selenium Yeast as a Source of Food-Form Organic Selenium

The fermenting yeast, *Saccharomyces cerevisiae* was reported as early as 1961 to assimilate inorganic Se from the culture medium and to convert it into SeMet [47]. In selenium-rich growing media, during synthesis of selenium S-containing methionine, Se substitutes for sulfur in the structure of methionine, thus forming SeMet, which becomes part of yeast protein. The selenium yeast is valuable in animal and human nutrition, because it contains Se-Met which is the predominant organic form of selenium produced by food-chain autotrophs such as most plants and certain blue-green algae [40, 48].

The first batches of Se yeast reached the marketplace in 1974 by the "Universal Foods (a leading producer of food yeast in the US in 1970s)" on initiative of "Nutrition 21 (a California-based nutritional supplement company)". The Se-yeast rapidly gained popularity as a feed additive, although it remained unapproved for this purpose until the year 2003, when Alltech, Inc. succeeded in having their product, "Sel-Plex", FDA approved for all animal species. The *Saccharomyces cerevisiae*, grown in a selenium-rich media, is now a recognized source of organic food-form selenium [48]. At present, several companies produce and market Se yeast, and it is the most widely used source of Se for human supplementation. Selenium yeast is also increasingly employed in animal nutrition, since its use is FDA-approved since 2003. The maximum amount of Se that a yeast cell can theoretically incorporate depends on its methionine content and can be in the order of 6000 ppm for replacement of Met by SeMet. However, such full replacement is not achievable in practice; the highest amount of Se in yeast achieved so far is about 3000 ppm. The commercial culture Se yeast is tuned to contain from 500 to 2000 ppm of Se, most of them containing about 1000 ppm [13, 40].

Inclusion of selenium yeast as a supplement in the animal diets not only benefits animal health and performance, but also offers an added nutritional benefit to human consuming food-animal products. The SeMet containing plant or yeast

protein consumed by animals can be also stored in animal protein, which can result in bioactive selenium content in meat, milk, and eggs with potential human health benefits. As a result, supplementation of animal diets with selenium yeast contributed to the development of selenium-rich functional foods, including selenium-enriched milk, eggs and meats for human consumption [49-52]. Pure selenomethionine is also known as a toxic substance. However, a fetal toxicity to an adult could be expected when oral intake of SeMet is as high as 1 g. Thus Se yeast poses no considerable serious toxicity threat because to obtain 1 g of SeMet, as much as 1 kg of Se yeast containing 1000 ppm SeMet would have to be ingested. The chronic toxicity of Se yeast has been reported to be lower compared to sodium selenite in experiments with young rats [53] and growing pigs [54]. However, young, growing animals could be less sensitive to chronically toxic levels of Se-Met because most of the ingested SeMet could be continuously incorporated into newly synthesized proteins and removed from circulation. The chronic toxicity of SeMet is still to be investigated and established. Nevertheless, the safety record of Se yeast is excellent. No cases of accidental Se poisoning have been reported over the last four decades of its use as a feed additive and in nutritional supplements.

2.5. Selenium Deficiency Versus Selenomethionine Deficiency

The fact that "Selenium Deficiency" is indeed "SeMet Deficiency" is a resolved issue in research, but it is still unresolved in applications. It is still very common that whenever low selenium levels or deficiency disorders related of this element are observed in animals and humans the term selenium deficiency instead of SeMet Deficiency is applied. A distinction between the two types of deficiencies is necessary because a failure to distinguish between the two may result in the adoption of the wrong treatment or prevention strategies. [55] studied the effect of source and the dosage of Se supplementation on Se in eggs and blood variables of poultry. After supplementing the diets for 56 d, they observed significantly higher Se levels in serum and egg for the Se-supplemented groups compared with the unsupplemented control. It was also noted that Se from the two organic sources, L-SeMet and Se-enriched yeast, was more bioavailable than the sodium selenite as evidenced by blood and egg Se levels. Within the organic Se sources, L-SeMet showed higher Se transfer to eggs than Se-enriched yeast.

In human, Keshan Disease (KD) is an excellent in this context. The KD has a complex etiology, it is an endemic and often manifests as cardiomyopathy primarily among infants and young women consuming exceptionally low-selenium wheat and corn produced in the selenium deficient regions of China. The initial approach of addressing KD during 1974-77 was largescale Se supplementation with 0·5–1 mg sodium selenite tablet per week. Although this approach tremendously reduced the disease incidence, the protection was not long-lasting. Low salt tolerance prevented the administration of sufficiently large doses of inorganic sodium selenite in the most vulnerable infants and small children, which acted as a barrier to protect them from KD by this approach. Implementing an alternate approach, [56] demonstrated much more substantial and sustainable increases of blood selenium levels could be achieved by supplementing with Se-Met instead of sodium selenite leading to the realization the selenium deficiency in the KD-endemic regions was indeed deficiency of organic SeMet rather than inorganic Se. From that point forward, it was emphasized that eating foods naturally rich in Se would be more effective than inorganic sodium selenite supplementation. This method also offered a better solution to the selenium deficiency disorders in the district of Chita, which is a low-selenium region of the former USSR, where they simply provided the people with Se-rich wheat imported from the USA [57].

2.6. Assessment of Selenium Nutritional Status in Animals

Assessment of Se nutritional status of animal assists in evaluating and ensuring neither deficiency nor toxicity potential exists. There are several recommendations with regards to the method of adequate assessment of Se nutritional status of animals. These include the use of selenium concentration in blood-serum/plasma (without cells), whole blood (with cells), and hepatic, renal and muscular tissues (but primarily liver tissues). Selenium status can also be assessed by determining glutathione peroxidase (GSH-Px) activity in whole blood.

Determination of selenium in blood and tissues provides a direct assessment of selenium status, whereas GSH-Px activity in whole blood provides an indirect assessment of selenium status. The assessment of selenium status by measurement of GSH-Px activity is based on its biological functions as antioxidant system of the animal. However, laboratories that offer GSH-Px analysis are limited and it is a more expensive and technically difficult procedure. Liver Se content is a good indicator of Se status, but one must obtain a liver tissue sample either by biopsy on a live animal or from a dead animal. It is well worth the cost to have liver mineral analyses completed on any animal that dies (young or old) as a routine monitor of nutritional status. Analyzing the Se concentration and GSH-Px activity in whole blood of 326 cattle from 30 herds in Czech Republic, [58] observed a close and significant correlation between these two variables ($r = 0.90$; $p < 0.01$). The regression line, defined by the equation $y = 6.44x + 21.4$, allowed the determination the GSH-Px activity of 665.4 μkat L^{-1} as equivalent to Se concentration in whole blood 100 μg L^{-1}. These levels were used in diagnosis of insufficient Se in cattle in the Czech Republic.

Most laboratories perform either serum or whole blood Se concentration analyses. Serum Se concentration reflects more acute or recent changes in Se nutrition, whereas whole blood Se reflects more chronic or historical Se status. In some animals the GSH-Px resides primarily in the red blood cells, where whole blood Se level serves a better assessment of Se status. In some other animals, more GSH-Px exists outside

the red blood cell, where serum Se level is more useful. Selenium concentrations in serum and whole blood in a given animal species also varies by age of the animal. [59] suggested that the adequate level of selenium in the whole blood of cattle is between 0.08and 0.16 mg L^{-1}. In serum/plasma, the appropriate level in plasma selenium has been reported to be between 51 and 85 µg L^{-1} [60]. According to National Research Council [61], a dietary intake of 0.5 mg/kg DM may be enough to achieve this adequate blood Se level. Generally, an increase in the concentration of selenium in the diet results in an increase of the selenium concentration in the serum within 2-6 days after intake [62, 63]. Selenium supplementation in diets usually results in an increase of the selenium content and GSH-Px activity in the blood of calves [64], heifers [65] and fattening bulls [66]. Such positive effects become more pronounced when Se is supplemented in organic form as compared to inorganic form [65, 67]. Generally, organic Se supplementation resulted in an estimated 20% increase Se level and 16% increase in GSH-Px activity in blood [68].

2.7. Efficacy of Various Types of Selenium Supplementation

Research works have reported evidence that the biological potency of organic Se-Met is much better than inorganic selenite. The most probable reason for this difference lies with the fact that Se-Met can reach the amino acid pool directly, whereas before inorganic selenite could be incorporated to the body proteins/enzymes, they require reductive transformation processes during their passage through the intestinal membranes. Availability of transporter molecules such as cysteine (Cys) or glutathione (GSH) determines the rates of these reductive transformation processes of selenite. In contrast, selenate is not as easily reducible as selenite. [69] reported that selenite is actively transported through the membranes of the small intestine as such and subsequently reduced primarily in the liver. Reduced inorganic selenite or selenate by cysteine (Cys) and glutathione (GSH) exist as selenodicystine and selenodiglutathione, respectively, forming exchangeable selenium pool. The reduced selenium species undergo further transformations to the forms needed for the biosynthesis of the ultimate form, selenoenzymes. In studies with New Zealand women, the selenium absorption from selenite reached 44–70%, compared to 96% from Se-Met [70, 71], while [72] observed 84% selenium absorption from selenite and 98% from SeMet. In addition to selenodicystine and selenodiglutathione, the Se-exchangeable pool contains numerous other selenium species, including endogenously synthesized selenoproteins (e.g. GSH-Px, selenoprotein P, etc), excretory selenium metabolites (such as the trimethylselenium ion), selenosugars, etc [50, 73-74]. The SeMet is not included, which explains why none of the selenite-derived selenium species in the Se-exchangeable pool are significantly retained in body proteins. Instead they are excreted with the feces, the urine, or are methylated and exhaled. Through another biological pathway, some of the selenium from the Se-exchangeable pool also reacts with arsenic, mercury, cadmium, and other toxic elements. These interactions are part of the natural toxic-element-detoxification processes and form soluble or insoluble metal selenides or protein complexes, which are stored in liver and kidneys. The selenium stored in this way is generally not reusable. If human or animal body is exposed to toxic elements in a continuous manner, a substantial proportion of consumed Se would be sequestered in the detoxification processes, leaving less Se for the primary beneficial bioactive functions [43].

3. Selenium Supplementation for Human Health

3.1. Background

Selenium was originally detected as a covalently bound component in mammalian glutathione peroxidase, an antioxidant enzyme [75-76]. Selenocysteine, the 21st amino acid, is the key component of several selenoproteins with enzymatic functions such as redox homeostasis, thyroid hormone metabolism, and protection from oxidative stress and inflammation [77]. There are 25 selenoproteins in humans including glutathione peroxidases, thioredoxin reductases, and iodothyronine deiodinases [4]. Selenium required for human health can be supplied through supplementation, diet and food fortification. Selenium supplementation has been shown to be involved in reduction of susceptibility to viral-induced cardiomyopathy experienced by patients with Keshan disease [78-79]. Recently, a 15 month old boy with dilated cardiomyopathy responded to six months of Se supplementation along with anti-failure therapy. Cardiac function, hair, skin and general health of the patient improved significantly indicating Se deficiency as the probable cause [80]. Selenium supplementation increased serum Se levels which decreased HIV viral loads in HIV infected men and women [81]. In the same way, Se supplementation increased serum Se levels, increased vigor and reduced anxiety of HIV infected patients [82]. However, these results are not sufficient enough to recommend Se supplementation in patients with HIV [83]. An inverse relationship was reported between dietary selenium intake and cancer mortality [84]. Daily supplementation with high selenium yeast also significantly lowered the cancer risk among US American men with low baseline selenium levels while another study found no association between plasma selenium level and prostate cancer risk [85-86]. The effectiveness of selenium supplementation might be influenced by the nature of the selenocompound used and its dose, the initial selenium status and the genetic background, the form of cancer and the time point of intervention [87]. It is important to note that Se supplementation has been associated with increased risk of type 2 diabetes especially in men with high baseline plasma Se [88-90]. Past studies have shown that inorganic selenium can enhance insulin sensitivity by mediating insulin-like

actions [91-92]. On the contrary, high plasma selenium was also associated with a decreased risk of onset of impaired fasting glucose or diabetes in men [93].

3.2. Selenium in the Human Diet

Even though supplementation may be beneficial for people living in environments with low Se in food crops and soil, diet is still the main source of Se for the human population [94]. Human Se requirements can be provided in regular consumption of food with high concentration of Se. Se occurs in both inorganic and organic forms but is predominantly present as selenomethionine (SeMet) in food of plant origin while those of animal origin contain both SeMet and selenocysteine (SeCys) [95-96]. The Se concentration of food of both plant and animal origin depends on the protein content [97-98] with organs such as kidney and liver having a potential to accumulate Se [99]. Animal products such as meat and fish tend to be richer in Se than plant materials [100]. The highest Se content in food is found in fish products (Table 1). Shrimp is one of the most important food sources of Se in the diet because it has a major ability to accumulate the element [98]. Seafood, meat products, cereals, and bread are the foods that mainly contribute to the daily dietary intake of Se in healthy individuals from South-eastern Spain due to their high Se concentrations and frequent consumption in the diet [101]. Wheat is an efficient accumulator of Se and one of the main sources of dietary Se for the human population [102]. Wheat is estimated to supply nearly half the Se utilized by most Australians [102]. Selenium levels ranging from 87.6 to737 ng g^{-1} were reported in meat, chicken, fish and eggs [103]. Selenium concentration in human milk is greater than in milk from animals such as sheep, goat and cow [104]. Fruits and fresh vegetables are poor sources of Se probably due to their low protein content [105]. However, vegetables such as broccoli, Brussel sprouts, cabbage, cauliflower, collards, mustards, garlic, chives and onions tend to have higher Se concentrations [106-107]. Protein-rich nuts such as pistachios, walnuts and Brazil nuts have high Se concentrations [106]. Selenium concentrations up to 3800 ng g^{-1} were reported for Brazil nuts [108].

Table 1. *Selenium content of food.*

Food	Saudi Arabia	Greece	Slovenia	Spain
Meat	0.22-0.66	71.7	35-128	NA
Egg	0.23	123	61-70	NA
Cereals	0.04-0.16	NA	NA	27.8
Legumes	NA	162.5	NA	112
Vegetables	0.001	6.5	0.3-76.7	NA
Fruits	0.067	3.4	0.6-11.6	295
Fish	NA	246	153-686	NA
Milk	NA	15.4	12.5	NA
Bread	NA	91.9	NA	NA
Units	µg/g	ng/g	ng/g	ng/g
References	Al-Ahmary, 2009	Pappa et al., 2006	Smrkolj et al., 2005	Diaz-Alarcon, 1996

3.3. Human Dietary Selenium Intake

The concentration of Se in food and amount of food consumed determines the dietary intake of Se [109]. The dietary intake of selenium varies considerably around the world (Table 2) because of the large variability in geochemistry which determines the selenium content of foods [110-111]. Different countries also have different cultural foods and staples in their diet which determines Se intake. In a bid to correct and prevent deficiency diseases associated with low Se status, many countries have estimated and recommended daily requirements for Se [95]. The recommendation for daily intake of Se is determined by each country based on levels that maximize the activity of glutathione peroxidase (GSH-Px) in plasma [112]. The recommended daily intake of Se varies with age, sex and reproductive condition of the female population. For example, the recommended dietary allowance for lactating women (70 µg day^{-1}) is greater than that of the pregnant women (60 µg day^{-1}) in the USA [113]. However, they are the same (30-70 µg day^{-1}) in some parts of Europe (Germany, Austria, Switzerland) [113].

The recommended daily intake of Se is much lower in children than adults regardless of country. It varies from 10-45 µg day^{-1}; 15-40 µg day^{-1}; 12-50 µg day^{-1} for children under the age of 14yrs in UK, USA and New Zealand/Australia respectively [113]. The recommended dietary allowance of 55 µg day^{-1} for adults in USA is slightly lower than the United Kingdom reference nutrient intake (RNI) of 75 µg day^{-1} for men and 60 µg day^{-1} for women while the World Health Organization/Food and Agriculture Organization/International Atomic Energy Agency (WHO/FAO/IAEA) recommended a minimal intake level of 40 µg Se day^{-1} for men and 30 µg Se day^{-1} for women [114]. The United Kingdom and other European countries have mean intake levels that are approximately half the RNI, while intakes of less than 19 µg Se day^{-1} for men and less than13 µg Se day^{-1} for women have been reported in some parts of China [114].

Table 2. *Daily Se Intake in different countries.*

Country	Se Intake (µg day^{-1})	References
Spain	15.4	Diaz-Alarcon et al., 1996
Croatia	27.3	Klapec et al, 1998
Brazil	37	Maihara et al., 2004

Country	Se Intake (μg day^{-1})	References
Greece	39.3	Pappa et al., 2006
Germany	38-47	Oster and Prellwitz, 1989
Belgium	60	Waegeneers et al., 2013
Netherlands	67	Foster and Sumar, 1997
Switzerland	70	Foster and Sumar, 1997
Slovenia	87	Smrkolj et al., 2005
Japan	82.7-118	Miyazaki et al., 2004
Saudi Arabia	75-122	Al-Ahmary, 2009
USA	90-134	Waegeneers et al., 2013

About a decade ago, the average daily intake of Se in China was 69.2 μg day^{-1} (79.9 and 53.1 μg day^{-1} in urban and rural areas, respectively) in adult women when analyzed by instrumental determination and 35.1 μg day^{-1} (36.7 and 32.7 μg day^{-1}) by Food Composition Tables-based estimation [115]. The differences in daily intake for China may be due to either a decrease in intake over the years or may be a reflection of the Se content of the soil which varies greatly across regions. China is known for having both Se deficient areas and seleniferous soils in different parts of the country. The mean dietary selenium intake in Belgium was calculated to be 60 μg day^{-1}, which is at the lower end but within the range recommended by the Superior Health Council in Belgium (60-70 μg day^{-1}), and adequate according to the 55 μg day^{-1} recommended by the Scientific Committee on Food (SCF) of the European Commission [116]. Daily Se intake below 55 μg day^{-1} was reported for European countries such as Greece, Turkey, Spain, Poland, Croatia and Austria while Switzerland and Netherlands had above 60 μg Se day^{-1} [109]. In Germany, the dietary selenium intake of men is 47 μg day^{-1} and that of women 38 μg day^{-1} (Oster and Prellwitz, 1989). Animal protein was the main source of dietary selenium in Germany accounting for 65.5% of the total selenium intake [117].

3.4. Recommended Daily Allowance (RDA) of Selenium Whether Current RDA Is Enough

In the US, the Food and Nutrition Board (FNB) at the Institute of Medicine of the National Academies (formerly National Academy of Sciences) developed the Dietary Reference Intakes (DRIs) in which the intake recommendations for selenium and other nutrients are provided [118]. The term "DRI" is the general term used for a set of reference values used for recommending and assessing nutrient intakes of healthy people, which can vary with age and between male and females. These values are as follows;

1) Recommended Dietary Allowance (RDA), which is the average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals in a defined group. 2) Adequate Intake (AI), a level established when evidence is insufficient to develop an RDA and is set at a level assumed to ensure nutritional adequacy. 3) Tolerable Upper Intake Level (TUL): maximum daily intake unlikely to cause adverse health effects. 4) Estimated Average Requirement (EAR), which is the average daily level of intake estimated to meet the requirements of 50% of healthy individuals. It is usually used to assess the adequacy of nutrient intakes in population groups but not individuals.

Table 3 lists the current RDAs and TULs (from food and supplements taking into account the amounts of selenium that are associated with hair and nail brittleness and loss) for selenium in micrograms (μg) as adopted by [118]. However, the FNB failed to specify the chemical form of selenium for supplementation and the maintenance of health in its recommendations despite the fact that the biological potency of organic (yeast) selenium is much better than inorganic selenite.

Table 3. *Recommended Dietary Allowances (RDAs) and Tolerable Upper Intake Levels (TULs) for selenium in mcg.*

Age	Male	Male	Female	Female	Pregnancy	Pregnancy	Lactation	Lactation
	RDA	TUL	RDA	TUL	RDA	TUL	RDA	TUL
Birth to 6 m	15[†]	45	15[†]	45				
7–12 m	20[†]	60	20[†]	60				
1–3 y	20	90	20	90				
4–8 y	30	150	30	150				
9–13 y	40	280	40	280				
14–18 y	55	400	55	400	60	400	70	400
19–50 y	55	400	55	400	60	400	70	400
51+ y	55	400	55	400				

Breast milk, formula, and food should be the only sources of selenium for infants.

For infants from birth to 12 months, the Food and Nutrition Board (FNB) established an AI for selenium that is equivalent to the mean intake of selenium in healthy, breastfed infants.

[†]Adequate Intake (AI). Note: For infants from birth to 12 months, the FNB established an AI for selenium that is equivalent to the mean intake of selenium in healthy, breastfed infants.

[43] argued that despite the existence of numerous credible scientific literature with suggestions of 200–300 μg day^{-1} as the optimal selenium intake for health maintenance, the currently adopted (by FNB) RDAs for selenium of 55 μg day^{-1} for men and women over 19 years of age, 60 μg day^{-1} for pregnant women, and 70 μg day^{-1} during breast feeding would have to be concluded either too low or clearly inadequate. The biological function of Se was initially assigned solely to its involvement in the activity of glutathione peroxidase (GSH-Px) selenoenzymes. Accordingly, the RDA values are based on the amounts of selenium theoretically needed by an adult of average weight to maximize GSH-Px activity. However, several other additional selenoenzymes have been discovered, some of

which, such as the thioredoxin reductases, require significantly higher selenium intakes than GSH-Px for their maximum activity. This necessitates an elevation of the RDAs. [119] reported the 'physiological selenium requirement' of 80 µg day^{-1} for men and 57 µg day^{-1} for men and women, respectively; the current RDAs are lower than these established requirements. The physiological selenium requirement, which represents the amount of selenium needed to maintain selenium balance in the body, a gradual depletion of selenium reserve in the body would occur due to constant adherence to the current RDAs.

[120] observed that pregnant women in China receiving 100 µg of supplemental Se day^{-1} for 6–8 weeks had significantly lower incidence of edema and hypertension. Low selenium intakes have been shown to increase the risk of toxemia, nephropathy, edema, pre-eclampsia, placenta retention, hypertension, and stroke. Low selenium intakes during pregnancy may also harm the fetus. [43] emphasized that the RDA of 60 µg Se day^{-1} for pregnant women may not provide sufficient protection against complications during pregnancy and at birth. Likewise the current RDAs for infants, children, adolescents, and pregnant and lactating women are also too low. A depletion of Se in the milk along with a depletion of selenium reserves in the body of the lactating women may often occur if the pertinent RDA of 70 µg Se/day is followed during the lactation period. [121] demonstrated that these declines were prevented with an intake of 100–200 µg Se day^{-1} in the form of organic selenium (as in Se-yeast).

Furthermore, the current RDAs for selenium are also problematic in the sense that they ignored the high affinity of selenium for a number of toxic metals such as mercury and cadmium, and of metalloids such as arsenic, and several others, which naturally occur and enter the human body in various ways. This property enables Se to function as a detoxifying agent of these toxic elements, but renders itself metabolically inactive in the other relevant biological processes. [43] Suggested that at an intake of 200–300 µg day^{-1}, the deleterious effects of these toxic elements the organism could be significantly counteracted as well as adequate selenium would be left available for its other biological functions.

4. Biofortification of Selenium in Food and Feed Crops

4.1. Background

Biofortification is the process of increasing the bioavailable concentrations of essential elements in edible portions of crop plants through the use of fertilizers (agronomic biofortification) or through crop selection or breeding (genetic biofortification) [102, 122]. Agronomic biofortification (Figure 3) involves the enrichment of soils with Se using Se fertilizers to correct and augment the deficiency of Se in soils. This is important because low dietary intake of Se has been associated with low Se status of the soil. Low Se status of the soil leads to low Se uptake by plants used as forage for animals or food for the human population. There is a wide variability in capability of different plant species to accumulate Se. Some plants are accumulators while some others are Se accumulators with a natural tendency to concentrate Se in their tissues. Selenium hyperaccumulators are able to accumulate greater than 1000 mg kg^{-1} Se in their shoots. Identification of key genes in Se hyperaccumulators may lead to future genetic engineering approaches [123]. Genetic engineering attempts to exploit genotypic variation in Se accumulation in crops to select or breed varieties with increased Se which will minimize the need to use Se fertilizers [122, 124]. It identifies key genes for Se accumulation or hyper-accumulation in plants, and delivers them to target plants or crops to improve their capacity of Se enrichment ([8]. Selenium biofortification efforts makes use of the natural variation in Se accumulation between plant species, and choose crop species that naturally tend to contain higher Se (and S) levels, such as Brassica and Allium species [15, 41].

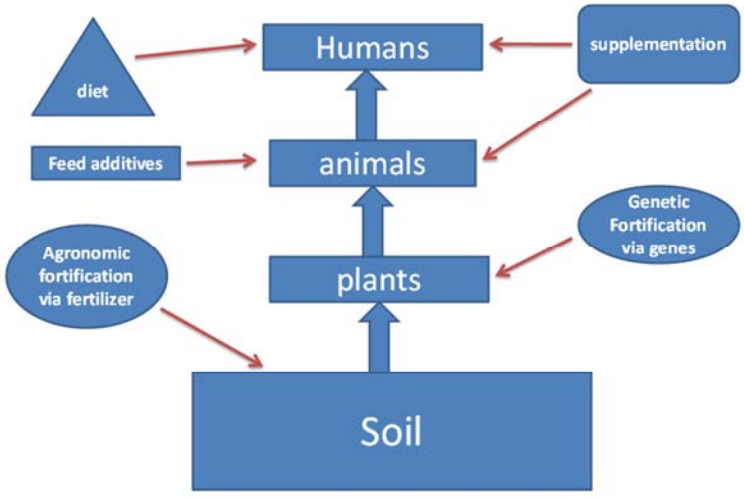

Figure 3. *Selenium transfer through the soil-plant-animal system.*

4.2. Genetic Biofortification

It is possible to enrich food crops in the longer term by selecting or breeding crop varieties with enhanced Se accumulation characteristics [122]. Genetic engineering has been used to produce new genotypes which are able to accumulate higher Se concentrations in bioavailable forms [15]. Genetic engineering of the S/Se assimilation pathway has been used to enhance plant Se tolerance, accumulation and volatilization [123]. Key genes for Se accumulation cloned from plants include Selenocysteine Methyltransferase (SMT), ATP Sulfurylase (APS), AtCpNifS, Glutathione Synthetases (GS), and Cystathionine-γ-synthase (CGS) (Guo et al., 2014). SMT transforms a large proportion of SeCys to non-poisonous MetSeCys which greatly reduces the chances of incorporation of SeCys and SeMet into protein which significantly increased Se tolerance in plants [125-126]. ATP Sulfurylase is a rate-limiting enzyme in Se metabolic pathways [8]. AtCpNifS can convert SeCys into Se and alanine by Selenocysteine lyase. Cystathionine-γ-synthase (CGS) is the key enzyme for methionine synthesis. Most of the work on genetic biofortification has been done with *Brassica juncea* probably because the species is an efficient Se accumulator and protein source for ruminants [127]. Overexpression of ATP sulfurylase (APS) in *Brassica juncea* resulted in the transgenic APS plants accumulating organic Se when supplied with selenate, while wildtype controls accumulated selenate. The transgenic APS plants also accumulated more Se than the controls [128]. Similarly when SeCys methyltransferase (SMT) was overexpressed in *A. thaliana* and *B. juncea*, SMT transgenics showed enhanced Se accumulation predominantly in organic form [129]. Double-transgenic plants (APS X SMT) accumulated up to 9 times higher Se levels than wild type [126]. Selenium accumulation in *Brassica juncea* was 2.3 times higher than that in the wild type plants when GS was incorporated [130]. Similarly, APS and GS transgenic Indian mustard plants accumulated 4.3 and 2.3 times higher Se in leaves than the wild type plants respectively [131]. CGS incorporation in transgenic *Brassica juncea* plants enhanced their tolerance and increased Se enrichment compared with the wild type plants [132].

4.3. Agronomic Biofortification

Both foliar application and fertilizer soil applications can be used to increase Se uptake in food crops or forages. Fertilizer application and foliar application of Brassica species with inorganic Se led to high accumulation of SeMet and its stability during processing [127]. Food fortified with selenium has proved to be more efficient than supplementation probably because they provide Se in a more bioavailable form. For example, selenium enriched garlic was more effective in the reduction of breast cancer development than selenium-enriched yeast [133]. [134] showed that foliar application of Se as potassium selenate is an efficient agronomic approach to improve seed Se concentration for lentil consumers. Results of their study showed that foliar application increased seed Se concentration from 201 to 2772 μg kg^{-1}. They reported that consumption of 20 g of biofortified lentil can supply all of the recommended daily allowance of Se. Consumption of Se-biofortified wheat was found to increase plasma Se concentration from a baseline level of 122 to 192 μg L^{-1}[135]. However, improvement of Se status by consumption of Se-biofortified wheat did not substantially modify the selected biomarkers of degenerative disease risk and health status in selenium replete cohort of healthy older men in South Australia. Substitution of Se-deficient wheat by wheat naturally enriched with Se and its products contributed to the increase of daily intake on the average by 18 μg (12–35 μg) in volunteers, which is more than 50% of the average daily intake. The increased Se intake induced an increase in GSH-Px activity in blood and decreased concentrations of TBARS, lipid parameters, and glucose in blood [136].

Rice produced in Italy is characterized by low content of selenium mostly due to the low content of selenium in soil of the production area [137]. Selenium food fortification was proposed as a strategy to counteract the inadequacy of selenium intake among the Italian population. Hence, a study was conducted to determine the effect of foliar fertilization of an Italian rice cultivar with sodium selenate on serum selenium. Selenium fortification of rice increased the serum selenium levels and GSH-Px activity after 20 days intake of this Se-enriched-rice [138]. Finland carried out a nationwide fertilization of their Se deficient soils by supplementing fertilizers with Se in the chemical form of sodium selenate due to an extremely low daily Se intake in the 1970s. This led to an increase of selenium concentration in cereals 15-fold compared with the level before the Se fertilization. The mean increase in the Se concentration in beef, pork and milk was 6-, 2- and 3-fold respectively. Consequently, the average dietary human intake increased from 40 μg Se day^{-1} in 1985 to a present plateau of 80 μg Se day^{-1}, which is well above the current nutrition recommendations [10]. The decline in Se daily intake in the UK from the 1970s to the 1990s was attributed to replacement of milling wheat having high levels of grain Se and grown on high Se soils in North America with UK sourced wheat having low levels of grain Se and grown on low-Se soils. Biofortification to enrich UK-grown food crops using Se fertilizers was proposed as the solution [122]. In Chile, endophytic bacteria (Acinetobacter sp. E6.2 and Bacillus sp. E5) has been shown to enhance Se content of food plants and can be used for biofortification of food crops in the Se deficient Chilean Andisols [139].

4.4. Food Fortification: Meat, Milk, and Eggs

The goal of food fortification is to increase the concentration of Se in food such as meat, milk and eggs by supplementation of basal diets or animal feeds. The response to supplementation of animal diets depends on the source and dose of Se [140]. Selenium can be supplied in animal diets

either as the organic or inorganic form. Inorganic forms of Se (such as selenates and selenites) and organic forms such as SeMet, SeCys and methylselenocysteine (MetSeCys) are widely used as nutritional selenium sources [141].

Feeding chickens up to 5.1 μg g^{-1} of inorganic and organic forms of Se did not affect egg production and the welfare of the laying hen [142]. This suggests that fortification with inorganic and organic sources of Se is a practical way of producing Se-enriched eggs for the consumers. It has been shown that egg selenium content can easily be manipulated to give increased levels, especially when organic selenium is included in hen's diet at levels that provide 30.5 mg kg^{-1} selenium in the feed [143]. Chickens are also a source of meat for the majority of human population. A study was conducted to investigate the effects of SeMet and sodium selenite supplementation on meat quality and antioxidant status in broilers. The results indicated that SeMet supplementation was more effective than sodium selenite supplementation for increasing Se in serum and tissues, enhancing antioxidant activities and reducing the drip loss of breast muscle [144]. In an experiment, dietary selenium-enriched probiotics (SP) supplementation increased the rate of egg laying, day egg weight, mean egg weight, egg Se content, and egg GSH-Px activity but also decreased the feed:egg ratio and egg cholesterol content. Results suggested that Se contents, GSH-Px activity, and Haugh units (HU) of eggs were affected by the dietary Se level, whereas the egg-laying performance and egg cholesterol content were affected by the dietary probiotics [145].

Se-enriched cow milk can be produced by varying dietary Se supplementation in the form of selenized yeast [146]. Dietary supplementation with Se yeast in lactating dairy cows increased Se milk concentrations in Australia [147]. In China, supplementation of diet with Se-enriched yeast was more effective than sodium selenite in producing favorable cow milk with high polyunsaturated fatty acids and Se concentrations [67]. In a similar study, Holstein cows' diet was supplemented with either Se yeast or selenite. Results showed that Se yeast may be more effective than sodium selenite in improving the antioxidant status and increasing the whole blood and milk Se concentrations of dairy cows [148]. A daily supplementation of 1-6 mg organic selenium to the feed of dairy cows increased the selenium content of milk from 8 μg kg^{-1} to 94 μg kg^{-1} in 8 weeks [96].

Selenium coming from inorganic forms is less efficiently absorbed and incorporated into milk compared with organic sources, probably due to its reduced bioavailability [149]. Supplementing dairy cow diets with organic Se not only increases Se concentration in milk, but also increase its bioavailability [146]. It has been estimated that selenium requirements could be met by the consumption of 2-3 dl selenium-enriched milk until the age of 8 and with 4-6 dl selenium-enriched milk until the age of 20 [96].

5. Conclusion

The amounts of Se required for animal and human health is supplied through food crops and forage which is in turn dependent on Se levels in the soil. This means that plant available Se in the soil determines the Se status of animals and humans which could be deficient, adequate or toxic. Recommended daily intake of Se is determined independently by each country and varies with age, sex and other factors. The recommended daily allowance (RDA) may not be adequate because other selenoenzymes have been discovered which require higher Se intake. Selenium requirements for animals and humans can be supplied through diet or supplementation. Selenium supplementation has been used to successfully treat patients with dilated cardiomyopathy, reduce HIV viral loads and has been shown to reduce cancer risk. Although supplements can be used as a remedy for Se deficiency, a well balanced diet with adequate Se can be used to prevent health problems associated with Se deficiency. Even though inorganic Se was approved as feed additives for livestock, Se-Met is the chief nutritional form of Se. Deficiency of Se-Met is often mistaken for Se deficiency because research has shown that Se-Met is more effective than inorganic selenite. Problems associated with the use of inorganic selenite as supplements include less efficient absorption, potential toxicity, low transfer to milk, meat and egg; and inability to build Se reserves in the body because of greater excretion. Food fortified with Se has been shown to be more efficient than supplementation. Fish and meat products contain higher Se than plant products with fish products having the highest Se content. Selenium content of food crops can be increased by agronomic bio-fortification which involves fertilization of soils and enrichment of animal feeds or basal diets. Addition of Se to fertilizers in Finland is an example of successful agronomic bio-fortification which has led to higher Se status in the human population. The fortification of animal feeds or basal diets with Se has also been successfully used to increase Se content of meat, fish, eggs and milk. Selenium content of food crops and forages can also be increased through genetic bio-fortification in which case key genes of Se hyperaccumulators are identified and manipulated to increase Se accumulation in plants. The efficient transfer of Se in the soil-crop-animal system is important for adequate human nutrition and health.

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