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Selenium (Se) Intake and Plasma Se Concentration in Low Soil-Se Countries -

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ABSTRACT

As a trace element Selenium (Se) is essential for maintaining the proper development and health of both animals and humans. Se enters the food chain through plants, which absorb it from the soil. Se is one of the elements with a remarkable regional variation in distribution and availability. Most European countries have low Se content in the soil and thus in agricultural crops. The countries with particularly low Se content in the soil include Finland, New Zealand and the Keshan region in China. Some states of the USA and Canada have high content of Se in the soil and hence the cereals grown there are rich in Se. The countries that imported cereals from these countries had relatively high Se intake and high Se levels in the blood. In the 1970s the Se content of domestic foods in Finland and New Zealand were very low with daily dietary Se intake of less than 25 µg/ day. In the Keshan region it was even lower. The low concentration of Se in the blood in Finland was the cause of high mortality from coronary heart disease and cardiovascular diseases. In New Zealand low concentration of Se in the feed was manifested by the high occurrence of the white muscle disease and pathological conditions of liver and heart in sheep and cattle. In China, Se deficiency was manifested by the occurrence of Keshan Disease (KD, cardiomyopathy) and Kashin Beck (osteoarthropathy). In order to increase the dietary Se intake of the population in Finland the government decided to supplement multinutrient fertilizers with sodium selenate. Within a short time, the content of Se in food products increased several times, dietary Se intake increased to around 100 µg/ day and plasma Se concentration increased to over 100 µg/ mL. In New Zealand, imports of selenium rich grains from Australia led to increased dietary intake of Se and Se concentration in plasma to values close to the recommended level of 100 µg/ mL. In the Keshan region of China researchers served sodium selenite to children, and in the mid-1970s, selenite was added to table salt. No significant outbreaks of KD occurred in the late 1970s.

INTRODUCTION

As a trace element Selenium (Se) is essential to the proper development and health of both animals and humans. As for animals, Schwarz and Foltz [1] have shown that Se prevents dietary necrotic liver degeneration in the rat. Further studies have shown it to prevent multiple necrotic degeneration (heart, liver, muscle, and kidney) in the mouse and exudative diathesis in the chick [2]. Since then work on farming animals has contributed to our understanding of how essential Se is for animals [3]. The role of Se in humans is less clear than in experimental and domestic animals. However, the essential role of Se in human nutrition and health is now well established. In the mid-1970s Schrauzer et al. [4] argued that low levels of Se in the blood were associated with greater susceptibility to cancer. Moreover, the detrimental effect of low blood Se levels on heart diseases and human cancer mortality has led some researchers to speculate that there may be a relationship between Se intake and the risk of cardiovascular diseases and cancer [5].

It is well known that in humans as well as in animals there is a direct relationship between daily Se intake and blood/tissue Se levels. Because of the large differences in the Se content in soils in various countries, the dietary Se intakes vary widely among residents in different parts of the world. Based on the Se content in the soil (without going into details), the world can be divided into countries rich in Se (Venezuela, several states in the USA, especially North and South Dakota, Enshi county, China) and poor in Se (Finland, New Zealand and Keshan disease areas) [6].

It has been shown that the soil of most European countries is poor in selenium [7]. Thus, the population consuming agricultural products grown in these areas has low dietary Se intake [8] and a low content of this element in the body [9]. Selenium accumulated in agricultural products enters the food chain. Suboptimal Se status has been reported to be widespread throughout Europe, the UK and the Middle East [10,11]. It is generally recognized that Se intakes across Europe are low, reflecting inadequate soil levels, particularly in Eastern Europe [9,10,12].

It is widely believed that the amount of dietary selenium intake should be such that its concentration in plasma/serum should be 100 µg/ L [13]. Such an amount is believed to be required for optimal activity of cytosolic glutathione peroxidase [14]. According to data collected since 1990 from more than a dozen European countries [15], the concentration of Se in plasma/serum was lower than 90 µg/ L. The countries where this concentration did not exceed 60 µg/ L were Czech Republic, Serbia, Croatia, Slovakia, UK, Sweden, France, Poland and Hungary [16]. Inadequate intake of Se and other microelements in adult and elderly population in several European countries has been demonstrated by other authors [17]. In many countries the daily Se intake was lower than 50 µg [16]. Data from publications originating primarily from Western Europe showed that there was a positive association between indicators of socioeconomic status and micronutrient intake and/or status [18].

In 1999, Duffield et al. [19] and Surai et al. [20] carried out a human study in which women and men were supplemented with placebo and increasing doses of selenium. The authors showed that an upper estimated requirement of 90 µg Se/ day was calculated as the intake necessary for maximization of plasma GSH-Px activity. A large body of evidence indicates that European intakes of selenium were falling. For example, in 1978 selenium intake in Britain was 60 µg/ day, seven years later it was only 43 µg/ day, and in 1990 it fell to 30 µg/ day. Even in 1997, the average reported selenium intake was only 43 µg/ day [20]. The fall in Se intake in this period was believed to have resulted from the reduced importation of North American (mainly Canadian) Se-rich wheat for bread making [21].

The results of research carried out in Poland from 1980 showed a drastic decrease in Se concentration in the blood components of adults. The concentration of Se in the plasma of healthy women in the period 1981-1999 was respectively: in 1981-83: 95 µg/ L; in 1990-91: 59 µg/ L and in 1997-99: 54 µg/ L [22]. The reason we think, was connected with the reduction in its intake related to the suspension of grain exports from North America to Poland, due to martial law [23].

In some European countries the daily Se intake was lower, a dozen to 40 µg/ day [20,22]. The main reason for this are the decreased imports of bread making wheat from North America which, in general, contains much more selenium than the wheat grown in the UK and in other European countries. Selenium content in the grains in the USA and Canada could be associated, in some parts of these countries, with the high selenium content in the soil. North American wheat contains on average over 10 times more selenium than British wheat [24]. According to some authors [25] surveys indicate that wheat is the most efficient Se accumulator of the common cereal crops (wheat,

rice, maize, barley, oats) and is one of the most important sources of selenium for human consumers. Importation of North American wheat was found to be an important beneficial factor affecting the blood selenium status in the residents. This has been demonstrated, inter alia, by Alfthan [26], who studied the change in Se status of a Finnish subpopulation between 1975 and 1984. During the 1970s, the low dietary intake of selenium, 25 µg/ day, corresponded to a plasma selenium level of 0.63-0.76 mmol/ L (49.7-60.0 µg/ L), being among the lowest values reported in the world [27]. The mean serum Se concentration varied between 52 µg/ L in 1977 to 99 µg/ L in 1982. The correlation between the estimated national Se intake and serum Se concentration was r = 0.89. The results demonstrate that the serum Se concentration increased due to the importation of Se-rich grain from North America.

Some authors maintain that although selenium intakes in Europe have fallen, they are still sufficient for any obvious signs of deficiency to appear [12]. It seems that such an opinion is not fully justified because in several studies it has been shown that in patients with diagnosed cancer of various organs Se concentration in the blood was significantly lower than in healthy people [20,28-32]. In addition, in many cases low plasma/serum selenium concentrations were found in women with complicated pregnancies [33-35]. These results seem to indicate that a higher concentration of Se in the blood prevents the development of the above-mentioned diseases and complications.

Several authors have shown that consumption of articles based on imported selenium-rich cereals contributed to the increase in the concentration of selenium in the blood components [14]. In most human diets, the main sources of Se are cereals, meats, fish, seafood, offal (kidney, liver) and milk products [10,12,36].

Selenium plays an important role in mammalian biology. Selenium is not, in itself, an antioxidant. It works through proteins to which it is incorporated in the form of Selenocysteine (Sec) called selenoproteins. So far 25 selenoproteins have been identified [37]. Some of them fulfill the role of antioxidants. The most important antioxidant enzymes in the body are: glutathione peroxidases (GSH-Pxs), thioredoxin reductases as well as Selenoprotein P (SePP). They protect the membranes against the damaging effects of reactive oxygen species [36,37]. Selenium level, GSH-Px activity and SePP concentration in mammals depend on the amount of Se intake in the diet [10,38,39]. Plasma GSH-Px activity and SePP concentration are considered to be markers of selenium status in the body [40]. It should be noted that SePP is a selenoprotein that has as many as 10 Sec residues in its chain and has two functions. Nine of Sec (at C-terminal domain) are responsible for transporting Se from the liver (where it is synthesized) to various organs, and only one (at N-terminal domain, position [40] has antioxidant properties [40], Suboptimal selenium intakes may reduce the synthesis of these selenoproteins which, in turn, might effect DNA damage, impair the immune system and anti-inflammatory responses, and reduce protection against diseases like cancer, heart disease, chronic kidney disease and others [12,41].

As mentioned above, the activity/concentration of selenoproteins depends on the concentration of Se in the organism. The low concentration of Se in residents of some countries is related to the consumption of articles grown in a region with low selenium content in the soil [27].

It should be noted that most Se ingested by animals and humans comes from the soil through plants. The levels of Se available in soils are highly variable globally. Areas that are notably low in Se include Finland, New Zealand, parts of China, Siberia and Tibet and some other areas in the world [42].

SELENIUM INTAKE AND BLOOD LEVELS IN FINISH POPULATION

Foods and feeds naturally grown in Finland were extremely low in Se which led to a high incidence of deficiency diseases in young animals and in humans. Salonen et al [43] studied selenium concentration in 11,000 persons in two counties in eastern Finland, an area with an exceptionally high mortality from Cardiovascular Diseases (CVD). The subjects were aged 35-59 years and had died of Coronary Heart Disease (CHD) or other CVD or had a non-fetal myocardial infarction during a seven-year follow-up. The mean serum selenium concentration for all cases was 51.8 µg/ L and for all controls 55.3 µg/ L ($P < 0.01$). Serum selenium of less than 45 µg/ L was associated with an adjusted relative risk of CHD death and other CVD. Similar studies conducted in this area showed that patients with diagnosed cancer had a significantly lower ($P < 0.012$) plasma Se concentration (50.5 µg/ L) compared with healthy controls (54.3 µg/ L) [44]. The results of these studies support the hypothesis that selenium deficiency increases the risk of CHD and certain cancers in middle-aged persons.

In order to increase the dietary Se intake of the population the Ministry of Agriculture and Forestry decided in 1984 to supplement multinutrient fertilizers with Se in the chemical form of sodium selenate [45]. Initially sodium selenate was added to multinutrient fertilizers used in agriculture and horticulture in amounts of 16 mg Se/ kg of fertilizer for cereals. In 1990 the quantity of Se was reduced to 6 mg/ kg of fertilizer. As a result of this procedure Se content in agricultural and animal products after three years increased several times [46]. The selenium concentration of spring cereals has increased on average 15-fold compared with the level before Se fertilization. The mean increase in Se concentration in beef, pork and milk was 6-, 2- and 3-fold [27].

Se supplementation of fertilizers affected the average intake significantly. A high plateau was reached during the years 1987-1990 of between 110 and 120 µg/ day [47] (Figure 1). This was reflected

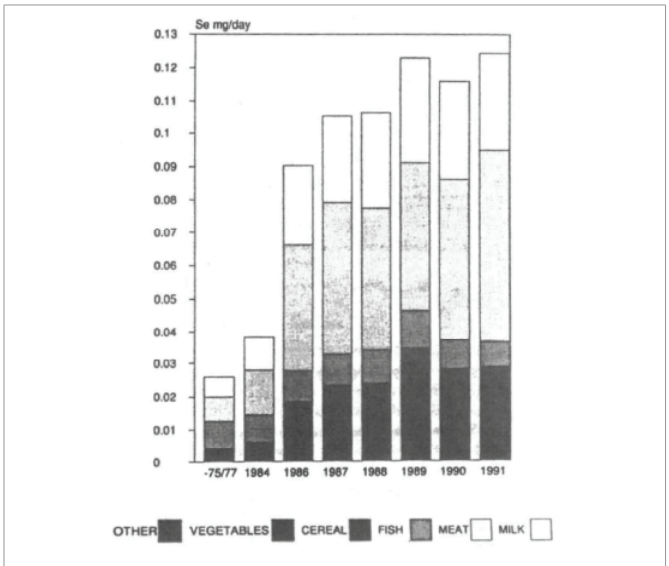

Figure 1: Average dietary selenium intake (energy level of 10 MJ) in Finland before and during selenium supplementation. Adapted from Varo et al. [46].

in plasma Se concentration. While before Se supplementation of fertilizers the mean plasma Se concentration was 0.89 mol/ L (70.3 µg/ L) after supplementation it reached its highest mean level four years later at 1.5 mol/ L (118.4 µg/ L). Since 2000, this level fluctuated within 100 µg/ L. In 2010 the mean plasma Se level reached the level of 1.4 mol/ L (110.5 µg/ L) [27] (Figure 2).

This level was still above the general plasma Se value in European countries [48], but equal to that found in Canada and the USA, where the daily Se intake was and is relatively high [48,49]. This indicates a good response to the supplemented fertilizers [50]. Although there is a certain trend in reducing mortality from coronary heart disease and cancer it is difficult to say clearly if this is an effect of increased Se intake or whether some other factors could be involved [47,50].

From Finnish research, Kivisaari and Vermeulen [51] draw the conclusions that selenium fertilization is a safe and economic way to increase the selenium in food and fodder. The response of plants to selenium fertilization is very accurate. The selenium level of the crop can be adjusted very accurately as required. The effect of fertilization is rapid, affecting also the Se content of milk, eggs and other foodstuffs originating from animals feeding on field crops.

With this method the whole population living is a selenium deficient area can be safely supplied with adequate selenium uptake.

Alfthan et al. [27] believe that as a result of research conducted in Finland on the effects of selenium added to fertilizers, the rates of cardiovascular diseases and cancers have remained similar during pre- and post-supplementation indicating medical and life-style factors to be much stronger determinants than selenium. Nationwide supplementation of fertilizers with sodium selenate is shown to be effective and safe in increasing the Se intake of the whole population. Also, the health of animals has improved.

SELENIUM INTAKE AND BLOOD LEVELS IN THE POPULATION OF NEW ZEALAND

New Zealand is another country with predominantly low Se environment, particularly the South Island [52] (Figure 3). The low content of Se in the soil and agricultural products was reflected in the high occurrence of the white muscle disease and pathological conditions of liver and heart in sheep and cattle (Figure 4). Robinson [52] writes that the analyses made in 1966 showed that the Se intake in New Zealand was 25 µg/day, about one-third of that estimated for residents in the United States. Se levels in blood and urine of New Zealand residents were low compared with those reported for persons living in Europe or North America [53].

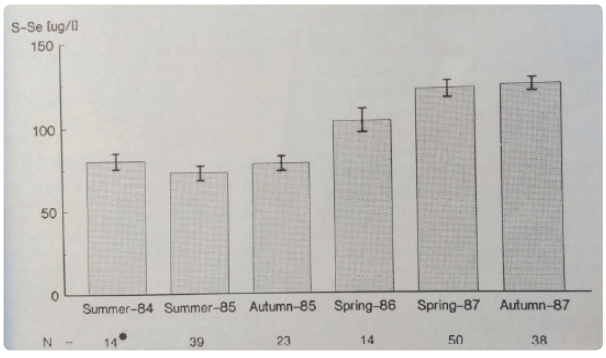

Figure 2: The mean values of selenium concentration in sera of the Helsinki area before and during selenium supplementation. Adapted from Mussalo-Rauhamaa et al. [47].

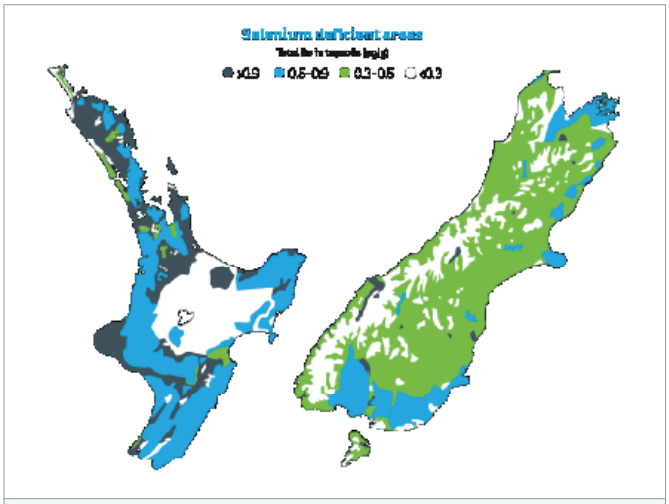

Figure 3: The content of selenium in the soil of New Zealand. The content of selenium in the soil is particularly low in the South Island (right). Taken from Wikipedia.

Figure 4: Lamb with muscular dystrophy caused by white muscle disease, showing posture with feet widespread, and prominent shoulder blades. Taken from Wikipedia.

A comparison of the group of older Dunedin adults studied in 1976 by Thomson's group revealed that plasma selenium levels increased from 37.1 to 67.1 µg/ L [54]. The authors state that the increase in selenium status of the adult population of New Zealand was most likely due to the importation of rich selenium cereal from Australia, supplementation of stock feed resulting in increased concentrations in meat and poultry, and the increase in consumption of fish, poultry, no refined cereal and legumes.

At the turn of 1980/1990 the selenium status of Otago residents clearly shows a gradual increase from a mean value of 0.86 µmol/ L (= 67.91 µg/ L) in 1988 to a mean value of 1.03 µmol/L (= 81.3 µg/ L) in 1991 and 1.19 µmol/ L (= 93.96 µg/ L) in 1992-3 [55].

Because people were eating products with high content of Se in the grain imported from Australia [56] the daily Se intake was relatively high. As a result, in the years 1977 – 2002, plasma Se concentration reached the values of 91 to 122 µg/ L [54].

Among the residents of New Zealand's North Island the concentration of Se in the blood was slightly higher than in South Island. In the years 1972-1980, among Hamilton residents the levels were 57 and 87 µg/ L, respectively [57]. These changes are consistent with the values calculated from variations in dietary intake of Se of wheat products from the blending of New Zealand wheat (11 ng Se/ g) with imported Australian wheat (150 ng Se/ g). Se concentrations

found in wheat products such as bread and flour were also in agreement with similarly calculated values. In contrast, the blood Se in residents of Dunedin and Tapanui, on the South Island of New Zealand, did not change with importation of wheat and coincided with the Hamilton minimum. This is attributed to the absence of wheat imports from Australia into the South Island, which produces over 90% of the New Zealand wheat crop [35].

In the 1996 report Thomson and Robinson [55] argued that supplementing wheat for human consumption with selenium-containing fertilizers, as has been practiced in Finland, or recommending dietary selenium supplements, may not be necessary for New Zealand. Increased intake of the foods that contain high levels of selenium seemed to be sufficient at that stage. Plasma Se concentration in older New Zealanders, in the years 2000, fluctuates within 100 µg/ L [58]. Plasma Se concentration of 100 µg/ L is believed to be required for optimal activity of glutathione peroxidase, the indicator of selenium repletion [15].

An interesting relationship between selenium intake and blood selenium level, based on several publications from New Zealand, was described by Thomson and Robinson [59]. Visitors and new settlers to New Zealand from the United States, the United Kingdom, Canada, Tahiti and Australia, where Se intakes were greater, arrive with blood Se typical of their own countries but which in time fell to the New Zealand range. Furthermore, New Zealanders traveling overseas were exposed to a greater intake and returned with raised blood Se which again gradually fell back to the New Zealand range.

SELENIUM INTAKE AND BLOOD LEVELS IN KESHAN REGION, CHINA

China is a country where Se concentration in the blood in humans varies from very low values to toxic concentrations. China's provinces with the very low concentration of Se in the blood were called Keshan areas. There are two diseases associated with selenium deficiency: Keshan Disease (KD; endemic juvenile cardiomyopathy) and Kashin-Beck Disease (KBD; osteoarthropathy). Keshan disease was identified in the winter of 1935 in northeast China [60].

The disease was named Keshan disease, because the first outbreak occurred in the Keshan county of Heilongjiang province. This disease occurs essentially in a wide belt-like region throughout mainland China, from northeast to southwest, and the low Se area (based on soil Se content) is also located in the same belt region (Figure 5). The causal relationship between Se deficiency and KD was established based on the low Se levels of local foods and low status of this nutrient in local residents [61].

KD affects mainly children below 15 years of age and women of child-bearing age [61]. KBD usually becomes evident between the ages of 5 and 15 years and occurs in China, Tibet, Siberia and North Korea [62] (Figure 6). The population living in these regions consume very low amounts of this element in the daily diet. Yang et al. [63] have calculated (based on determination of Se content in food items) that the daily Se intake of different age groups (3 to 56 years) of residents in KD affected and nonaffected areas was 3.1-7.7 µg and 5.3-19.1 µg/ day, respectively. As a result the plasma concentration of Se was lower than 5 µg/ L, and in many cases, it was even undetectable. Rarely did the concentration achieve the values of 15 µg or more [64]. Due to the low concentration of Se in the blood of patients with KD and KBD, it has been suggested that Se deficiency is a fundamental risk factor of these diseases. It is believed that in addition to selenium

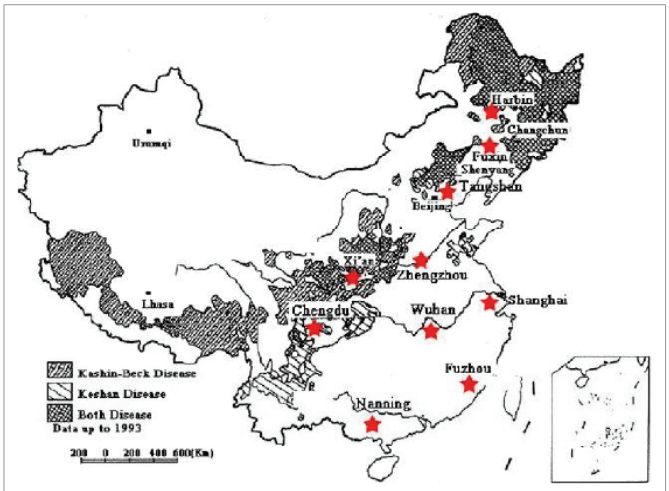

Figure 5: Distribution of KD and, KBD in China, including the study areas within the survey (designated with red stars) Taken from Wikipedia.

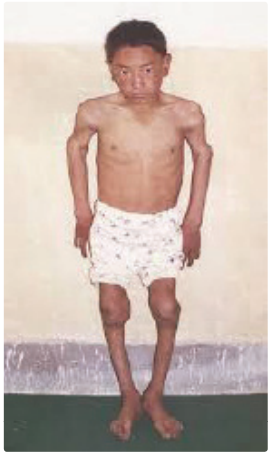

Figure 6: Kashin-Beck Disease: a permanent and disabling osteoarticular disease involving growth and joint cartilage. Taken from Wikipedia.

deficiency high concentration of organic matter in drinking water, and contamination of food by mycotoxins were the main factors in the etiology of the diseases [64,65].

Se concentrations of whole blood collected from residents in endemic sites were significantly ($P < 0.01$) lower than those in non-affected areas, with a cut-off point at 20 µg/L. Whole blood GSH-Px activity shows that in children in the endemic sites it was significantly ($P < 0.01$) lower than those in the non-endemic sites [60].

In 1974 to 1977, in several provinces of the Keshan region, children were given selenium (sodium selenite) or placebo once a week, depending on age: 0.5 mg (1-5 years) or 1.0 mg (6-9 years) [60,61]. In 1974, in the group of several thousand children supplemented with selenium and placebo, the incidence of KD was 2.2 ‰ and 13.5% respectively. In 1977 there were no cases among the 12,747 treated subjects and only 5 cases occurred among the placebo treated children [61].

In the mid-1970s, selenite was added to table salt (sodium selenite fortified salt). Studies on the incidence of Keshan disease carried out in 11 high-incidence areas have shown a significant decrease in the occurrence of Keshan disease. In 1989 only 58 cases were reported in all of China and in 1990 only 45 [66]. The preventive effect of Se-

fortified table salt against KD was tested on 1.05 million people with another 0.6 million people as the control group. The average annual incidence of acute and subacute types of the disease significantly decreased from 25.23 to 2.7 per 100,000 in the Se-supplemented population, while the corresponding rate in the controls decreased from 19.76 to 7.36 per 100,000. Furthermore, the detection rate of new cases of a latent type of KD in the Se-supplemented group (0.18%) was significantly lower than that in the control group (1.07) [67]. After oral administration of sodium selenite and Se-fortified table salt as preventive measures, the GSH-Px activity of healthy children in the endemic sites increased to levels comparable to those of children in the non-endemic sites [60,68]. Significant correlation was found between Se levels of blood and GSH-Px activity (r = 0.57). According to a literature review presented by Chen [60] no significant outbreaks of KD occurred in the late 1970s.

In conclusion, in countries where the soil contains low selenium, also cultivated agricultural products are poor in this element. The population consuming these items has a low selenium intake which, in turn, may be linked with various diseases of people and animals. There are various tools/ways leading to the increase of selenium intake: application of selenium to fertilizers, import of selenium-rich cereals, addition of selenium to table salt and other items. Each of these approaches leads to the increase of the selenium intake. The countries mentioned in this article applied different tools and each of them led to an increase in selenium intake and an increase in the concentration of this element in the body. As a result, disorders associated with selenium deficiency cease to exist.

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