18 Selenium

18.1 Introduction

Selenium (Se) is derived from the Greek word *selene* meaning moon goddess. It was discovered by Jacob Berzelius of Sweden in 1817. In the 1950s, grazing animals suffering from disorders manifested as muscular dystrophy and liver necrosis were corrected with selenium supplementation. Selenium in humans is mainly present as selenocysteine that is responsible for the functions of numerous mammalian proteins. The first selenoprotein to be identified was glutathione peroxidase (GSHPx) in 1973, which catalyzes the breakdown of toxic hydroperoxides. There are four antioxidant glutathione peroxidases that are capable of reducing a variety of organic hydroperoxides to their corresponding alcohol. In this role, Se is an essential component of the body's antioxidant defense system

Selenoprotein P that contains 60% of plasma selenium, is a selenoprotein whose exact function in unknown, but it may function as a transport protein for selenium or it may act as an extracellular antioxidant. Another selenoprotein known as Type 1 iodothyronine-5-deiodinase (ID-I), is an enzyme required for the removal of iodine from thyroxine (T_4) to produce triiodothyronine (T_3). Selenium deficiency in animals causes abnormally high plasma T_4 levels and decreased plasma T_3 levels. This function of selenium has important implications for the interpretation of the effects of selenium deficiency when vitamin E levels are adequate. In particular, decreased growth and susceptibility to cold stress during prolonged selenium deficiency may relate to altered thyroid hormone metabolism.

Other functions of Se that currently cannot be explained by its presence in the known selenoproteins include the metabolism of drugs, maintenance of plasma glutathione levels, an involvement in the function of the 'neutrophil' white blood cells of the immune system, and some involvement in lipid and glucose metabolism.

18.2 Food sources

Environmental conditions and agricultural practices have a profound influence on selenium content of many foods. Grains and sources of nuts and seeds grown in soils with high selenium content are good plant sources of selenium.

Fish, meat (especially organ meats) eggs, milk and shellfish are good animal sources of selenium. Foods providing the highest nutrient density for selenium (mcg/kcal) are tuna, whole wheat bread, hams, eggs, oatmeal, white bread and related flour-based products, beef and chicken (Table 18.1). In general, the higher the protein content of a food, the more selenium it contains. Selenium is obtained in diet as seleno-amino acids, primarily selenomethionine and selenocysteine. Selenium is lost from foods during milling in processing or during boiling in cooking.

Table 18.1 Selenium content of various food items

Food	µg
Brazil nuts, dried 1 oz	840
Bun, tuna 1 piece (68g)	81.6
Wheat flour, whole meal 1 cup	53
Tuna,canned in oil, drained, 3 1/2 oz	48
Roti prata with egg, 1 piece	38.3
Noodles, enriched, boiled,1 cup	35
Guava, green skinned, raw, flesh only 12 g	34
Macaroni and cheese (box mix), 1 cup	32
Bread, fiber increased, white, toasted 2 slices	32
Thosai, masala, 1 piece	31.7
Macaroni, elbow, enriched, boiled, 1 cup	30
Spaghetti w/meat sauce, 1 cup	25
Chicken, meat only, 1/2 breast	24
Bread, enriched, whole wheat, 2 slices	20
Roti prata, 1 piece	17.5
Oatmeal, 1 cup cooked	16
Egg, raw, whole, 1 large	15
Bread, enriched, white, 2 slices	14
Rice, enriched, cooked, 1 cup	14
Cottage cheese, low fat 2%, 1/2 cup	11
Walnut, black, dried, 1 oz	5
Cheddar, black, dried, 1 oz	4

Source : HPB (2003)

18.3 Deficiences

The status of selenium in humans can be assessed by plasma selenium concentration, which indicates short-term status (days), and erythrocyte Se concentration, which indicates long-term status (weeks to months). There are no 'normal' reference ranges as values vary between countries.

The signs and symptoms of selenium deficiency in animals and humans include muscle pain, muscle wasting and cardiomyopathy, a form of heart disease. These same symptoms are seen when there is insufficient selenium in total parenteral nutrition solutions. Farm animals in areas with low soil concentration of Se (e.g. New Zealand and Finland) and humans in certain areas in China develop characteristic heart disorders associated with an inadequate selenium intake, known as Keshan Disease. Although selenium is protective against the development of the disease, it cannot correct the heart disorders once they have occurred.

The best documented cases of selenium deficiency involve children and adults who are undergoing long-term parenteral nutrition and receiving nutritional feedings containing no selenium. The clinical manifestations of Se deficiency include muscle pain and weakness, cardiomyopathy, and a loss of pigmentation, described as pseudoalbinism. Decreased selenium concentrations and GSHPx activity in plasma and various tissues were found in most cases. Treatment with selenium has proved effective in correcting the disorder.

Epidemiological studies have demonstrated an increased incidence of several kinds of cancers in people living in areas with low selenium levels in the soil. Selenium intake and plasma selenium levels also appear to be inversely correlated with cancer mortality. This suggests that selenium may be a naturally occurring 'anticarcinogen' able to provide protection against the development of cancer, a conclusion supported by some studies in laboratory animals. The mechanism of action is not known, but it seems possible that selenium-containing enzymes may be involved in the detoxification of the carcinogens (Diwadkar-Navsariwala & Diamond, 2004).

Some population surveys have indicated an association between a lower antioxidant intake with higher incidence of heart disease. The oxidized form of low density lipoprotein (LDL) promotes plaque build-up in coronary arteries. Selenium is one of a group of antioxidants that may help limit the oxidation of LDL-cholesterol and thereby help prevent coronary heart disease. However, more research are needed to establish clear relationships between risk of CVD and low selenium and the antioxidant vitamins.

Surveys of patients with rheumatoid arthritis, a chronic disease that causes pain, stiffness, swelling and loss of functions in joints, have indicated that they have reduced selenium levels in their blood. Selenium as an antioxidant, may help control levels of free radicals and help to relieve symptoms of arthritis. However, more clinical studies are needed in this area.

18.4 Factors affecting selenium requirement

Most dietary selenium is highly bioavailable, varing between 50% and 80%. Selenomethionine, which is estimated to account for at least half of the dietary selenium, is absorbed by the same mechanism as methionine, and its selenium is made available for selenoprotein synthesis when it is catabolized via the transsulfuration pathway. The bioavailability of selenium in the form of selenomethionine is greater than 90 percent. The selenium in selenocysteine, another significant dietary form, is also highly bioavailable. There appear to be some minor dietary forms of selenium (especially present in fish) that have relatively low bioavailability, but these forms have not been identified. Selenate and selenite, two inorganic forms of selenium, have roughly equivalent bioavailability which generally exceeds 50 percent. Although they are not major dietary constituents, these inorganic forms are commonly used as selenium supplements.

The requirement for selenium increases with age and growth processes. For women, the requirement during pregnancy is about double the amount of selenium required by adult women who are not pregnant. During lactation, the amount is even higher due to increased requirement. There was also a report from China, during the outbreak of the Keshan Disease that women of childbearing age were more susceptible to developing the disease. There were however no additional reports on this gender effect.

Adequacy of vitamin E has been said to be able to compensate for lack of selenium, as vitamin E can perform the functions of an antioxidant, just as selenium. On the other hand, free radicals produced by polluted environment tend to increase the need for selenium as an antioxidant to protect against cell damage. Similarly, smokers have a higher requirement for selenium. Studies have shown that low dietary selenium intake is a risk factor for lung cancer.

18.5 Setting requirements and recommended intakes of selenium

In Malaysia, hardly any nutritional study on the status of selenium has been carried out. Similarly, data on selenium content of Malaysian foods are equally lacking. Hence, in setting recommended intakes for Malaysians, the TSC on Minerals had refered to several major publications, namely the FAO/WHO Expert Consultation report of 2002, the DRI Committee of IOM (2000) and the WHO/FAO/IAEA (1996). The rationale and steps taken in setting requirements and the levels recommended by these organisations were considered. The TSC decided to adapt the approach and the recommendations of FAO/WHO (2002) as the revised RNI for Malaysia, given in bold in the following paragraphs according to age groups and summarised in Appendix 18.1.

Infants

No functional criteria of selenium status have been demonstrated that reflect response to dietary intake of infants. Thus the IOM (2000) had based the recommended intakes of selenium on adequate intake that reflects the observed mean selenium intake of infants fed principally with breast milk. Assuming an average selenium concentration of milk of well-nourished but unsupplemented mothers to be 18 g/l and the average volume of human milk to be 0.78 l, the adequate intake of selenium for this age group would be 14 µg/day, rounded to 15 µg by the DRI Committee. For the older infants, the IOM report had computed the adequate intake based on selenium in human milk plus that in infant foods. The computed intake was 20 g per day.

A similar approach was taken by FAO/WHO (2002) although the actual intakes recommended were lower than those of the IOM. The Consultation felt that the estimates of RNI for infants are compatible with estimates of the international reference range of the selenium content of breast milk (18.5 µg/l) with data from an extensive international survey of breast milk selenium of WHO-IAEA and with WHO data on the milk

consumption of exclusively human-milk-fed infants in developed and developing countries. Data from the WHO-IAEA survey from six countries suggest that the human milk from all countries met the RNI for infants aged 0–6 months. In two of six countries, Hungary and Sweden, the human milk selenium was marginal with respect to the RNI for infants aged 7–12 months.

The TSC on Minerals had recommended that intakes for infants 0-5 months and 6-11 months be calculated based on the WHO/FAO estimated selenium requirements of 0.85 µg/kg/day and 0.91 µg/kg/day, respectively, whilst making use of the reference weight for Malaysian infants.

RNI for infants

0 – 5 months	**6 µg/day**
6 – 11 months	**9 µg/day**

Children

The IOM (2000) found no data that could be used to derive an estimated average requirement for selenium for children or adolescents. In the absence of additional information, the requirements and recommended intakes for children and adolescents were estimated based on extrapolation from adult values. The requirement was thus based on the same criteria of adequacy as adults, that of selenium intakes that would be expected to maximize plasma glutathione peroxidase activity.

In the case of the FAO/WHO consultation, recommended intakes for children were calculated based on the factors derived from studies done in Keshan, China, on the basis of body weight and a factor to allow for growth. Thus, for children 1-3 years, 4-6 years and 7-9 years, the estimated selenium requirements are 1.13 µg/kg/day, 0.92 µg/kg/day and 0.68 µg/kg/day, respectively (FAO/WHO, 2002). The TSC then used the reference weight for Malaysian children to compute the RNI for selenium for these age groups.

RNI for children

1 – 3 years	**17 µg/day**
4 – 6 years	**21 µg/day**
7 – 9 years	**22 µg/day**

Adolescents

The requirement for selenium is calculated as in children on the basis of body weight and a factor to allow for growth. If the protein requirement for the adolescent is adequate, then automatically the selenium needs will be met. For male and female adolescents 10-18 years, the estimated selenium requirements are based on 0.50

µg/kg/day and 0.42 µg/kg/day, respectively (FAO/WHO, 2002) and the body weights of adolescents from local data.

RNI for adolescents

Boys	**10-18 years**	**28 µg/day**
Girls	**10-18 years**	**23 µg/day**

Adults and elderly

IOM (2000) had determined the estimated requirements for selenium for adults based on the results of two intervention studies that were done in different countries but with similar designs. The Chinese study (Yang *et al*., 1987) suggests that a plateau of plasma glutathione peroxidase activity was reached with a selenium intake of 41 µg/day. The New Zealand study (Duffield et al., 1999) seem to suggest an estimated requirement of 38 µg/day. The DRI Committee took the average of these two studies and made a weight adjustment for North American males and arrived at a requirement of 45 µg/day. The RDA, computed as 120% of the requirement, is 55 µg for both men and women. For the elderly group, IOM did not recommend for additional intakes, noting that the aging process does not appear to impair selenium absorption or utilization.

Studies have been conducted with adult male subjects initially of low selenium status given a carefully monitored diet providing selenium at 11 µg/day together with supplements of selenomethionine given orally which provided 0, 10, 30, 60, or 90 µg/day. Starting at frankly deficient levels, total daily selenium intakes of above 41 µg/day were found sufficient to increase plasma GSHPx substantially and to saturate plasma activity in 60-kg male subjects within 5–8 months. It was estimated that satisfactory levels of plasma selenium and of GSHPx indicative of adequate selenium reserves would be attained after intakes of approximately 27 µg/day by 65-kg male subjects (WHO/FAO/IAEA, 1996). Such criteria satisfying the definition of average normative requirements for selenium was used as the basis for calculating recommended nutrient intake (RNI) values by the FAO/WHO consultation after interpolating estimates of average requirements by allowing for differences in weight and basal metabolic rate of age groups to up to 65 years. A 25 percent increase (2 x assumed SD) was next added to allow for individual variability in the estimates of RNI.

The FAO/WHO (2002) estimated selenium requirement for adult men, 19-65 years of age is 0.42 µg/kg/day, while those > 65 years old is 0.41 µg/kg/day. For adult women (19-65 years and > 65 years), the requirement is set at 0.37 µg/kg/day. Thus, using reference body weights of 62 kg and 55 kg for adult Malaysian men and women (19-65 years) and 57 kg and 49 kg for older men and women (>65 years) respectively, the TSC on Minerals had recommended that the Malaysian RNI for selenium for men and women are as follows.

RNI for adults

Men	**19 – 65 years**	**33 µg/day**
Women	**19 – 65 years**	**25 µg/day**

RNI for elderly

Men	**> 65 years**	**29 µg/day**
Women	**> 65 years**	**23 µg/day**

Pregnancy

Upon reviewing the literature, IOM (2000) found few studies that could provide information on the selenium requirements of pregnant women. However, the pregnancy requirement should allow accumulation of enough selenium by the fetus to saturate its selenoproteins. Based on an estimated foetal deposition of 4 µg/day throughout pregnancy, the estimated requirement is increased by this amount during pregnancy. Since most selenium is highly bioavailable, no adjustment for absorption is felt necessary.

WHO/FAO/IAEA (1996) attempted to predict the increase of dietary selenium needed for pregnancy by factorial estimation of the likely quantity of selenium incorporated into the tissues of the foetus. It was assumed that the total products of conception amount to 4.6–6 kg lean tissue with a protein content of approximately 18.5–20 percent. If the selenium content of this protein resembles that of a skeletal muscle, growth of these tissues could account for between 1.0 and 4.5 µg/day of selenium. With an assumed asbsorption and utilization rate of 80 percent dietary selenium and allowing for a variability of estimates (CV 12.5 percent) an increase of 2 µg/day was felt appropriate for the second trimester and 4 µg/day for the third trimester of pregnancy (FAO/WHO, 2002).

RNI for pregnancy

1st trimester	**25 µg/day**
2nd trimester	**27 µg/day**
3rd trimester	**29 µg/day**

Lactation

Based on an estimated human milk selenium concentration of about 18 µg/l and a milk volume of 0.78 l per day, the average amount of selenium secreted in milk was estimated by the DRI committee to be 14 µg. Since most selenium in human milk is present as selenomethionine, which has a bioavailability of greater than 90%, no adjustment was made for absorption. The IOM (2000) hence added 14 µg /day of selenium to the estimated requirement of nonpregnant and nonlactating women.

FAO/WHO (2002) estimated selenium requirement for lactating women from the estimated RNI for infants aged 0-6 months and 7-12 months. Assuming that the selenium of maternal milk is used with an efficiency of 80%, an individual variability of 12.5% and an estimated RNI for 0-6 months as 6 µg/day, the increase in maternal dietary selenium for the first 6 months of lactation is 9 µg/day. Using similar calculations, the increase in dietary selenium intake for months 7-12 is recommended to be 16 µg/day.

RNI for lactation	
0 - 3 months	**34 µg/day**
4 - 6 months	**34 µg/day**
7 - 12 months	**41 µg/day**

Discussions on revised RNI for Malaysia

In general, the recommended selenium intakes for most age groups by IOM (2000) are 1.5 – 2.0 times more than the values recommended by FAO/WHO (2002). The differences could be due to the different approaches in estimating physiologic selenium requirement by both committees. The approach used by the Malaysian RNI committee to derive the recommended selenium intakes is similar to that of FAO/WHO (2002). However, for most age groups, the Malaysian RNI values are slightly lower than those in the FAO/WHO report due to the lower reference body weights of Malaysians (Appendix 18.1).

18.6 Toxicity and tolerable upper intake levels

Excess intake of selenium can be toxic. Daily intakes of as low as 2-3 mg (~ 35 times US RDA) can cause toxicity symptoms if taken for many months. This has to be taken into consideration with the practice of healthy populations taking mineral supplements without expert advice. Toxic symptoms that manifest in selenosis include a garlicky odour of the breath, hair loss, nausea, diarrhoea, fatigue and changes in fingernails and toenails. Rashes and cirrhosis of the liver may also develop.

Upper tolerable nutrient intake level (UL) for various age groups as suggested by IOM (2000) are given in Table 18.2. FAO/WHO (2002) has also proposed a UL of 400 µg/day for adults. This proposed UL value for adults is felt to be able to provide a fully adequate margin of safety.

Table 18.2 Tolerable Upper Intake Level for selenium according to age groups

Age groups	µg/day of selenium
Infants	
0-6 months	45
7-12 months	60
Children	
1-3 years	90
4-8 years	150
9-13 years	280
Adolescents 14 – 18 years	400
Adult women ≥19 years	400
Adult men ≥ 19 years	400
Pregnant women	
14-18 years	400
19-50 years	400
Lactation women	
14-18 years	400
19-50 years	400

(Source: IOM, 2000)

18.7 Research recommendations

The following priority areas of research are recommended:

- Assessment of selenium intakes among the various ethnic, socioeconomic, age and gender groups
- Bioavailability studies of selenium from the local food sources.
- Cross-sectional and longitudinal studies on the prevalence of selenium deficiency in the population.
- Relationship between low Se intake and diet related chronic diseases.
- Influences of soil composition and agricultural practices on selenium content of plant foods and animal tissues. The information can then be used to document selenium content in local foods.

18.8 References

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Appendix 18.1 Comparison of recommended intake for selenium: RNI Malaysia (2005), RNI of FAO/WHO (2002) and RDA of IOM (2000)

Malaysia (2005)		FAO/WHO (2002)		IOM (2000)	
Age groups	**RNI (µg/day)**	**Age groups**	**RNI (µg/day)**	**Age groups**	**AI (µg/day)**
Infants		Infants		Infants	
0 – 5 months	6	0 – 6 months	6	0 – 6 months	15
6 – 11 months	9	7 – 11 months	10	7 – 12 months	20
					RDA (µg/day)
Children		Children		Children	
1 – 3 years	17	1 – 3 years	17	1 – 3 years	20
4 – 6 years	21	4 – 6 years	21	4 – 8 years	30
7 – 9 years	22	7 – 9 years	21		
Boys		Boys		Boys	
10 – 18 years	28	10 – 18 years	34	9 – 13 years	40
				14 – 18 years	55
Girls		Girls		Girls	
10 – 18 years	23	10 – 18 years	26	9 – 13 years	40
				14 – 18 years	55
Men		Men		Men	
19 – 65 years	33	19 – 65 years	34	19 – 30 years	55
> 65 years	29	> 65 years	34	31 – 50 years	55
				51 – 70 years	55
				> 70 years	55
Women		Women		Women	
19 – 65 years	25	19 – 65 years	26	19 – 30 years	55
> 65 years	23	> 65 years	26	31 – 50 years	55
				51 – 70 years	55
				> 70 years	55
Pregnancy		Pregnancy		Pregnancy	
1st trimester	25	1st trimester	26	14 – 18 years	60
2nd trimester	27	2nd trimester	28	19 – 30 years	60
3rd trimester	29	3rd trimester	30	31 – 50 years	60
Lactation		Lactation		Lactation	
0 – 3 months	34	0 – 3 months	35	14 – 18 years	70
4 – 6 months	34	4 – 6 months	35	19 – 30 years	70
7 – 12 months	41	7 – 12 months	42	31 – 50 years	70