SUMMARY

Selenium functions through selenoproteins, several of which are oxidant defense enzymes. The Recommended Dietary Allowance (RDA) for selenium is based on the amount needed to maximize synthesis of the selenoprotein glutathione peroxidase, as assessed by the plateau in the activity of the plasma isoform of this enzyme. The RDA for both men and women is 55 μg (0.7 μmol)/day. The major forms of selenium in the diet are highly bioavailable. Selenium intake varies according to geographic location, but there is no indication of average intakes below the RDA in the United States or Canada. A study done in Maryland reported that adults consumed an average of 81 μg (1.0 μmol)/day of selenium (Welsh et al., 1981). A Canadian survey reported selenium intakes of 113 to 220 μg (1.4 to 2.8 μmol)/day (Thompson et al., 1975). The Tolerable Upper Intake Level (UL) for adults is set at 400 μg (5.1 μmol)/day based on selenosis as the adverse effect.

BACKGROUND INFORMATION

Most selenium in animal tissues is present as selenomethionine or selenocysteine. Selenomethionine, which cannot be synthesized by humans and is initially synthesized in plants, is incorporated randomly in place of methionine in a variety of proteins obtained from plant and animal sources. Selenium is present in varying amounts in these proteins, which are called selenium-containing proteins.
Selenomethionine is not known to have a physiological function separate from that of methionine.

Selenocysteine is present in animal selenoproteins that have been characterized (see below) and is the form of selenium that accounts for the biological activity of the element. In contrast to selenomethionine, there is no evidence that selenocysteine substitutes for cysteine in humans.

Function

Selenium functions largely through an association with proteins, known as selenoproteins (Stadtman, 1991), and disruption of their synthesis is lethal for embryos (Bösl et al., 1997). A selenoprotein is a protein that contains selenium in stoichiometric amounts. Fourteen selenoproteins have been characterized to date in animals. The four known selenium-dependent glutathione peroxidases designated as GSHPx 1 through 4 defend against oxidative stress (Flohe, 1988). Selenoproteins P and W are postulated to do so as well (Arteel et al., 1998; Burk et al., 1995; Saito et al., 1999; Sun et al., 1999). Three selenium-dependent iodothyronine deiodinases regulate thyroid hormone metabolism (Berry and Larsen, 1992). Three thioredoxin reductases have been identified (Sun et al., 1999). Their functions include reduction of intramolecular disulfide bonds and regeneration of ascorbic acid from its oxidized metabolites (May et al., 1998). The selenium-dependent isoform of selenophosphate synthetase participates in selenium metabolism (Guimaraes et al., 1996). Other selenoproteins have not yet been characterized to the same extent with respect to function (Behne et al., 1997). Thus, the known biological functions of selenium include defense against oxidative stress, regulation of thyroid hormone action, and regulation of the redox status of vitamin C and other molecules.

Physiology of Absorption, Metabolism, and Excretion

Absorption

Absorption of selenium is efficient and is not regulated. More than 90 percent of selenomethionine, the major dietary form of the element, is absorbed by the same mechanism as methionine itself (Swanson et al., 1991). Although little is known about selenocysteine absorption, it appears to be absorbed very well also.

An inorganic form of selenium, selenate ($\text{SeO}_4^{2-}$), is absorbed almost completely, but a significant fraction of it is lost in the urine before it can be incorporated into tissues. Another inorganic form
of selenium, selenite (SeO$_3^{2-}$), has a more variable absorption, probably related to interactions with substances in the gut lumen, but it is better retained, once absorbed, than is selenate (Thomson and Robinson, 1986). Absorption of selenite is generally greater than 50 percent (Thomson and Robinson, 1986). Although selenate and selenite are not major dietary constituents, they are commonly used to fortify foods and as selenium supplements.

**Body Stores**

Two pools of reserve selenium are present in humans and animals. One of them, the selenium present as selenomethionine, depends on dietary intake of selenium as selenomethionine (Waschulewski and Sunde, 1988). The amount of selenium made available to the organism from this pool is a function of turnover of the methionine pool and not the organism’s need for selenium.

The second reserve pool of selenium is the selenium present in liver glutathione peroxidase (GSHPx-1). In rats, 25 percent of total body selenium is present in this pool (Behne and Wolters, 1983). As dietary selenium becomes limiting for selenoprotein synthesis, this pool is downregulated by a reduction of GSHPx-1 messenger ribonucleic acid (RNA) concentration (Sunde, 1994). This makes selenium available for synthesis of other selenoproteins.

**Metabolism**

Selenomethionine, derived mainly from plants, enters the methionine pool in the body and shares the fate of methionine until catabolized by the transsulfuration pathway. The resulting free selenocysteine is further broken down with liberation of a reduced form of the element, which is designated selenide (Esaki et al., 1982). Ingested selenite, selenate, and selenocysteine are all apparently metabolized directly to selenide. This selenide may be associated with a protein that serves as a chaperone (Lacourciere and Stadtman, 1998). The selenide can be metabolized to selenophosphate, the precursor of selenocysteine in selenoproteins (Ehrenreich et al., 1992) and of selenium in transfer RNA (Veres et al., 1992), or it can be converted to excretory metabolites (Mozier et al., 1988), some of which have been characterized as methylated forms.

**Excretion**

The mechanism that regulates production of excretory metabolites has not been elucidated, but excretion has been shown to be responsible for maintaining selenium homeostasis in the animal
(Burk et al., 1972). The excretory metabolites appear in the urine primarily, but when large amounts of selenium are being excreted, the breath also contains volatile metabolites (e.g., dimethylselenide) (McConnell and Portman, 1952).

**Clinical Effects of Inadequate Intake**

In experimental animals, selenium deficiency decreases selenoenzyme activities, but if the animals are otherwise adequately nourished, it causes relatively mild clinical symptoms. However, certain types of nutritional, chemical, and infectious stresses lead to serious diseases in selenium-deficient animals. For example, induction of vitamin E deficiency in selenium-deficient animals causes lipid peroxidation and liver necrosis in rats and pigs and cardiac injury in pigs, sheep, and cattle (Van Vleet, 1980). Another example of this phenomenon is the conversion of a nonpathogenic strain of coxsackie B3 virus to a pathogenic one that causes myocarditis when it infects selenium-deficient mice (Beck and Levander, 1998).

Keshan disease, a cardiomyopathy that occurs only in selenium-deficient children, appears to be triggered by an additional stress, possibly an infection or a chemical exposure (Ge et al., 1983). Clinical thyroid disorders have not been reported in selenium-deficient individuals with adequate iodine intake, but based on observations in Africa, it has been postulated that infants born to mothers deficient in both selenium and iodine are at increased risk of cretinism (Vanderpas et al., 1992).

Kashin-Beck disease, an endemic disease of cartilage that occurs in preadolescence or adolescence, has been reported in some of the low-selenium areas of Asia (Yang et al., 1988). It is possible that this disease, like Keshan disease, occurs only in selenium-deficient people. However, there has been no demonstration that improvement of selenium nutritional status can prevent Kashin-Beck disease, so involvement of selenium deficiency in its pathogenesis remains uncertain.

These considerations indicate that selenium deficiency seldom causes overt illness when it occurs in isolation. However, it leads to biochemical changes that predispose to illness associated with other stresses.

**SELECTION OF INDICATORS FOR ESTIMATING THE REQUIREMENT FOR SELENIUM**

A search of the literature revealed several indicators that could be considered as the basis for deriving an Estimated Average Require-
ment (EAR) for selenium in adults. These included prevention of Keshan disease or various chronic diseases; concentration of selenium in blood, hair, and nails; concentration of selenoproteins in blood; and urinary excretion of the element.

Keshan Disease

Keshan disease, a cardiomyopathy that occurs almost exclusively in children, is the only human disease that is firmly linked to selenium deficiency (Keshan Disease Research Group, 1979). In addition to a low selenium intake, low blood and hair selenium concentrations are associated with Keshan disease. The disease occurs with varying frequency in areas of China where the population is severely selenium deficient (Ge et al., 1983). Based on these observations, the occurrence of Keshan disease in a population would indicate that the population is selenium deficient.

Selenium in Hair and Nails

Although the forms of selenium in hair and nails have not been characterized, some correlations between dietary intake of the element and hair and nail concentrations of selenium have been demonstrated. However, the use of hair and nail selenium as markers of selenium status has been limited because factors such as the form of selenium fed, the methionine content of the diet, and the color of the hair affect the deposition of selenium in these tissues (Salbe and Levander, 1990). In addition, some shampoos in the United States and Canada contain selenium. Therefore, only well-controlled studies can make use of hair and nail selenium concentrations, and these markers are of little value in determining selenium requirements across population groups.

Selenium in Blood

Several forms of selenium are present in blood and in metabolizing tissues; thus, they can be discussed together. Physiologically active forms include the selenoproteins and some as yet uncharacterized forms that are present in low abundance. These forms of selenium are under physiological regulation. Within a specific range of dietary selenium intakes, selenoprotein concentrations are a function of selenium intake. Above this range of intakes, selenoprotein concentrations become regulated only by genetic and environmental factors. This lack of selenium effect implies that the selenium
requirement for selenoprotein synthesis has been met (Yang et al., 1987). At this plateau point, human plasma selenoproteins contain 0.8 to 1.1 \( \mu \text{mol/L} \) (7 to 9 \( \mu \text{g/dL} \)) of selenium (Hill et al., 1996). Thus, when tissue concentrations of selenium are below the level at which selenoproteins have plateaued, it can be stated with confidence that selenium supplies are limiting. Under these conditions, tissue (plasma) concentrations of the element are useful as indices of nutritional selenium status.

Above plateau concentration, however, the chemical form of selenium ingested and other factors become important in determining the tissue selenium concentration. Tissue (plasma) concentrations of selenium do not always correlate with selenium intake under these conditions (concentration greater than the plateau). As stated earlier, much of the dietary selenium supply is selenomethionine, which is synthesized by plants and appears to enter the methionine pool in animals where it is incorporated into protein randomly at methionine sites. Since selenomethionine is not subject to homeostatic regulation, blood levels of selenium will generally be higher when this form is consumed (Burk and Levander, 1999). The selenium released by the catabolism of selenomethionine will be present as selenocysteine in selenoproteins.

Based on these considerations, plasma selenium concentration has utility in assessing selenium intake of all forms of the element only when it is less than 0.8 \( \mu \text{mol/L} \) (7 \( \mu \text{g/dL} \)). Such values indicate that the synthesis of selenoproteins has not yet plateaued. Above these values, the plasma selenium concentration is highly dependent on the chemical form of the element ingested.

**Glutathione Peroxidases and Selenoprotein P in Blood**

Several selenoproteins are present in blood. Plasma contains the extracellular glutathione peroxidase (GSHPx-3) and selenoprotein P. Erythrocytes and platelets contain the most abundant form of selenium-containing glutathione peroxidase, intracellular glutathione peroxidase (GSHPx-1). Other selenoproteins have not been identified in blood. All three of these blood selenoproteins (GSHPx-3, selenoprotein P, and GSHPx-1) have been used to assess selenium status, but plasma GSHPx-3 has been preferred in recent years because its determination is more accurate than the determination of the erythrocyte enzyme GSHPx-1. Since hemoglobin interferes with the measurement of GSHPx-1 in the erythrocyte, use of this marker is problematic and consequently few data are available that can be used to set a selenium requirement. Also studies indicate
that plasma GSHPx-3 activity reflects the activity of tissue selenoenzymes better than does GSHPx-1 activity in erythrocytes (Cohen et al., 1985).

The limited information available on selenoprotein P indicates that it is the major form of selenium in plasma and suggests that it will be as good an indicator of selenium status as plasma GSHPx-3 (Hill et al., 1996). However, since an assay for it is not widely available at present, the data for selenoprotein P are insufficient to use it to estimate a dietary requirement.

**Cancer**

In some animal models, high selenium intakes reduce the incidence of cancer (Ip, 1998). In these studies, selenium was fed in amounts greater than that needed to support maximum concentrations of selenoproteins. In humans, some but not all observational studies have shown that individuals who self-select diets that produce high plasma and nail selenium tend to have a lower incidence of cancer (Clark et al., 1991).

Randomized trial data are limited to three studies, one conducted with poorly nourished rural Chinese (Blot et al., 1995), another with U.S. patients with a history of treated nonmelanoma skin cancer (Clark et al., 1996), and a third with participants in the Health Professional Follow-up Study (Yoshizawa et al., 1999). In the China trial, among eight combinations tested, subjects assigned a daily combination of selenium (50 µg [0.6 µmol]), β-carotene (15 mg), and α-tocopherol (30 mg) achieved a significant (21 percent) decrease in gastric cancer mortality, resulting in a significant 9 percent decline in total all-cause mortality. However, these results cannot be attributed to selenium alone, because the individuals consumed selenium in combination with β-carotene and vitamin E.

In the second trial, 200 µg (2.5 µmol)/day of selenium administered in the form of yeast showed no effect on recurrence of nonmelanoma skin cancer compared to a similar placebo group (Clark et al., 1996). Although the numbers of subjects were small (1,312 patients randomly assigned to the supplement or a placebo, ≈75% male) and the outcomes not prespecified, significantly lower rates of prostate, colon, and total cancer were observed among those assigned to the selenium group.

Similar prostate cancer results were reported from a nested case-control design within the Health Professionals Follow-up Study; the risk of prostate cancer for men receiving 200 µg (2.5 µmol)/day of selenium was one-third that of men receiving the placebo (Yoshizawa-
wa et al., 1999). The inverse association seen between the selenium level in toenail clippings and the risk of advanced prostate cancer was not confounded by age, other dietary factors, smoking, body mass index, geographic region, family history of prostate cancer, or vasectomy.

Results of these three studies are compatible with the possibility that intakes of selenium above those needed to maximize selenoproteins have an anticancer effect in humans. These findings support the need for large-scale trials. They can not, however, serve as the basis for determining dietary selenium requirements at this time.

Other Measurements

Urine

Attempts have been made to use urinary selenium excretion as an index of selenium status. While excretion of the element is proportional to selenium status, excretion is also sensitive to short-term changes in selenium intake (Burk et al., 1972). Thus, urinary excretion in selenium deficiency may reflect immediate selenium intake more than nutritional selenium status. This limits the utility of urinary selenium measurements.

Labeled Selenium

Uptake of selenium-75 (\(^{75}\)Se) by erythrocytes in vitro has been studied (Wright and Bell, 1963) as an indicator of selenium status. Although this method showed validity in sheep (Wright and Bell, 1963), its value in other species, including humans, has not been demonstrated (Burk et al., 1967).

FACTORS AFFECTING THE SELENIUM REQUIREMENT

Bioavailability

Most dietary selenium is highly bioavailable. 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 (Esaki et al., 1982). The bioavailability of selenium in the form of selenomethionine is greater than 90 percent (Thomson and Robinson, 1986). The selenium
in selenocysteine, another significant dietary form, is also highly bioavailable (Swanson et al., 1991). 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 (Cantor and Tarino, 1982). Selenate and selenite, two inorganic forms of selenium, have roughly equivalent bioavailability which generally exceeds 50 percent (Thomson and Robinson, 1986). Although they are not major dietary constituents, these inorganic forms are commonly used as selenium supplements.

**Gender**

Earlier reports from China (Ge et al., 1983), from a time when selenium deficiency was more severe than in recent years, indicated that women of childbearing age were susceptible to developing Keshan disease, whereas men were resistant. However, cases of the disease reported in the past 20 years appear to be limited to children, with equal prevalence in boys and girls (Cheng and Qian, 1990). Thus, a gender effect in susceptibility to this disease may be present at extremely low selenium intakes, but no such effect has been demonstrated at current intakes. Given women’s apparently increased susceptibility to Keshan disease, selenium requirements for the various age groups are based on male reference weights.

**FINDINGS BY LIFE STAGE AND GENDER GROUP**

**Infants Ages 0 through 12 Months**

*Method Used to Set the Adequate Intake*

No functional criteria of selenium status have been demonstrated that reflect response to dietary intake in infants. Thus, recommended intakes of selenium are based on an Adequate Intake (AI) that reflects the observed mean selenium intake of infants fed principally with human milk.

Human milk is recognized as the optimal milk source for infants throughout at least the first year of life and is recommended as the sole nutritional milk source for infants during the first 4 to 6 months of life (IOM, 1991). Therefore, determination of the AI for selenium for infants is based on data from infants fed human milk as the principal fluid during periods 0 through 6 and 7 through 12 months of age. The AI is the mean value of observed intakes as calculated
from data on the selenium content of human milk and other studies which estimated the volume typically consumed as determined by test weighing of infants in the age category. In the age group 7 through 12 months, an amount is added for the contribution to intake of selenium obtained from weaning foods.

Average selenium concentrations of human milk consumed by infants at different ages are shown in Table 7-1. In general, the selenium content of human milk is highest in colostrum (33 to 80 µg [0.4 to 1.0 µmol]/L) (Ellis et al., 1990; Higashi et al., 1983; Hojo, 1986; Smith et al., 1982), whereas concentrations in transitional milk at 1 week (18 to 29 µg [0.2 to 0.4 µmol]/L) are less than half those of colostrum (Ellis et al., 1990; Higashi et al., 1983; Hojo, 1986). There is wide interindividual variation in the selenium content of human milk (Higashi et al., 1983), and the selenium content of hind milk (milk at the end of an infant feeding) is greater than that of the fore milk (milk at the beginning of the feeding) (Smith et al., 1982).

Selenium is also present in human milk in extracellular glutathione peroxidase (GSHPx-3) (Avissar et al., 1991), but the distribution of selenium among milk proteins needs further characterization. It is also likely that a large and variable fraction of milk selenium is present as selenomethionine substituting for methionine as has been described for plasma.

The average selenium content of mature human milk sampled between 2 and 6 months lactation appears to be relatively constant within a population group (Debski et al., 1989; Funk et al., 1990). However, human milk selenium varies with maternal selenium intake. Selenium concentrations in mature human milk in Finnish women consuming 30, 50, or 100 µg (0.4, 0.6, or 1.3 µmol)/day of selenium were 6, 11, or 14 µg (0.08, 0.14, or 0.18 µmol)/L of selenium, respectively (Kumpulainen et al., 1983, 1984, 1985). Other studies reported average selenium concentrations of mature human milk of 10 to 23 µg/L (with a range of 6 to 39 µg/L) (Cumming et al., 1992; Debski et al., 1989; Ellis et al., 1990; Funk et al., 1990; Higashi et al., 1983; Hojo, 1986; Levander et al., 1987; Mannan and Picciano, 1987; Smith et al., 1982).

The average selenium content of human milk from mothers in Canada and the United States was 15 to 20 µg (0.19 to 0.25 µmol)/L (Levander et al., 1987; Mannan and Picciano, 1987; Smith et al., 1982). An older study analyzed human milk samples from women living in 17 states in the United States. The authors reported mean milk selenium values to be 28 µg (0.35 µmol)/L in areas with high soil selenium content and 13 µg (0.16 µmol)/L in areas with low
<table>
<thead>
<tr>
<th>Reference</th>
<th>Selenium Content of Milk (µg/L)</th>
<th>Stage of Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shearer and Hadjimarkos, 1975</td>
<td>18 (7–60)</td>
<td>17–869 d</td>
</tr>
<tr>
<td>Smith et al., 1982&lt;sup&gt;a&lt;/sup&gt;</td>
<td>41.2 ± 17.3</td>
<td>1–4 d (colostrum), from a different sample of women</td>
</tr>
<tr>
<td></td>
<td>18 ± 3.8</td>
<td>1 mo</td>
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<td></td>
<td>15.7 ± 4.6</td>
<td>2 mo</td>
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<td></td>
<td>15.1 ± 5.8</td>
<td>3 mo</td>
</tr>
<tr>
<td>Higashi et al., 1983&lt;sup&gt;b&lt;/sup&gt;</td>
<td>80 (35–152)</td>
<td>Day 1 (colostrum)</td>
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<tr>
<td></td>
<td>29 (15–79)</td>
<td>1 wk (transitional milk)</td>
</tr>
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<td></td>
<td>18 (9–39)</td>
<td>1 mo</td>
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<td></td>
<td>17 (6–28)</td>
<td>3 mo</td>
</tr>
<tr>
<td></td>
<td>18 (9–33)</td>
<td>5 mo</td>
</tr>
<tr>
<td>Kumpulainen et al., 1983</td>
<td>10.7 ± 1.6 (SD&lt;sup&gt;c&lt;/sup&gt;)</td>
<td>1 mo</td>
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<tr>
<td></td>
<td>5.8 ± 1.2</td>
<td>3 mo</td>
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<tr>
<td></td>
<td>5.6 ± 0.4</td>
<td>6 mo</td>
</tr>
<tr>
<td>Kumpulainen et al., 1984</td>
<td>11.8 ± 1.7</td>
<td>1 mo</td>
</tr>
<tr>
<td></td>
<td>10.9 ± 1.9</td>
<td>2 mo</td>
</tr>
<tr>
<td></td>
<td>10.0 ± 1.9</td>
<td>3 mo</td>
</tr>
<tr>
<td>Kumpulainen et al., 1985</td>
<td>13–14</td>
<td>2 mo</td>
</tr>
<tr>
<td>Hojo, 1986&lt;sup&gt;e&lt;/sup&gt;</td>
<td>34.2 ± 12.8</td>
<td>4 d (colostrum)</td>
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<tr>
<td></td>
<td>24.0 ± 4.2</td>
<td>7–8 d (transitional milk)</td>
</tr>
<tr>
<td></td>
<td>22.5 ± 4.2</td>
<td>36–86 d</td>
</tr>
<tr>
<td>Levander et al., 1987</td>
<td>20 ± 1 (SEM&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>1 mo</td>
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<tr>
<td></td>
<td>15 ± 1</td>
<td>3 mo</td>
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<tr>
<td></td>
<td>15 ± 1</td>
<td>6 mo</td>
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### Maternal Selenium Intake (µg/d) | Methods
---|---
Not reported | *n* = 241 mothers from 17 states, ages 17–44
Not reported | *n* = 8 human milk-fed infants and their mothers who provided 72 milk samples. Stage of lactation and time of day had no effect on milk Se.
Not reported; thought to be comparable to American intakes | *n* = 22 Japanese healthy full-term infants and their mothers, aged 22–34. Women were from the same geographical area. Wide interindividual variation in milk Se content. Also measured serum level: mean serum level in mothers at 3 mo pp = 14.8 ± 4.7 µg/dL; level in control subjects = 13.5 ± 1.9 µg/dL.
50 (average Finnish dietary selenium intake) | *n* = 46 human milk samples from 31 Finnish mothers.
100 (yeast-Se supplement) | *n* = 200 Finnish healthy full-term infants and their mothers. Three groups: no supplement, 100 µg/d yeast-Se, and 100 µg/d selenite. Highest milk content values were found in the yeast-Se group. In the no-supplement group, the peak milk content (7.2) was reached at 6 mo pp.
Not reported | *n* = 5 Japanese healthy full-term infants and their mothers, aged 25–28. Also measured GSHPx levels in milk. GSHPx levels were highest in colostrum and decreased with increasing time of lactation. Urinary Se was not associated with milk Se or GSHPx.
84 ± 4 84 ± 4 87 ± 4 | *n* = 23 lactating mothers with healthy full-term deliveries, aged 18–36. Also examined 13 nonlactating women. Dietary intake was based on duplicate food and drink composites and food records.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Selenium Content of Milk (µg/L)</th>
<th>Stage of Lactation</th>
</tr>
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</table>
| Mannan and Picciano, 1987<sup>a</sup> | 15.6 ± 0.4 (fore)  
18.1 ± 0.6 (hind) | 4, 8, 12, and 16 wk |
| Debski et al., 1989<sup>a</sup> | 22.2 ± 0.8 (SEM)  
16.8 ± 1.3 | Any 9 consecutive mo during 1–26 mo lactation |
| Ellis et al., 1990 | 32.8 ± 3.2  
26.4 ± 1.6  
24.0 ± 1.6  
21.6 ± 1.6 | 3 d  
7 d  
21 d  
42 d |
| Funk et al., 1990 | 15.5  
21.3  
17.8  
19.7 | 1–6 mo (rainy season)  
1–6 mo (dry season)  
13–19 mo (rainy season)  
13–19 mo (dry season) |
| Cumming et al., 1992 | 11.9 ± 3.5 (SD) | 6–12 wk |
| Jochum et al., 1995 | 9.9 ± 0.5 | 4 mo |

<sup>a</sup> Hind milk selenium concentration greater than that in fore milk.  
<sup>b</sup> Lack of correlation between human milk and serum selenium concentration.  
<sup>c</sup> SD = standard deviation.  
<sup>d</sup> pp = postpartum.
### Maternal Selenium Intake (µg/d) and Methods

<table>
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<tr>
<th>Intake</th>
<th>Methods</th>
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<tbody>
<tr>
<td>Not reported</td>
<td></td>
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<tr>
<td>10 healthy mothers with normal term pregnancies, mean age = 30</td>
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<tr>
<td>Values from weeks 4, 8, 12, and 16 were pooled</td>
<td></td>
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<tr>
<td>No Se supplements taken during pregnancy or lactation</td>
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<tr>
<td>Measured GSHPx in milk—similar pattern as milk Se</td>
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<tr>
<td>Also looked at plasma and erythrocyte levels of Se and GSHPx</td>
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<tr>
<th>Intake</th>
<th>Methods</th>
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<tbody>
<tr>
<td>101 ± 6 (vegetarians)</td>
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<tr>
<td>n = 26 vegetarian and 12 nonvegetarian healthy lactating mothers, mean age = 29</td>
<td></td>
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<tr>
<td>Dietary intake based on 2-d intake records</td>
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<tr>
<td>Milk Se content is based on undialyzed milk; values for dialyzed milk samples were similar for both vegetarians and nonvegetarians</td>
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<th>Intake</th>
<th>Methods</th>
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<tr>
<td>106 ± 5 (nonvegetarians)</td>
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<tr>
<td>n = 26 vegetarian and 12 nonvegetarian healthy lactating mothers, mean age = 29</td>
<td></td>
</tr>
<tr>
<td>Dietary intake based on 2-d intake records</td>
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<tr>
<td>Milk Se content is based on undialyzed milk; values for dialyzed milk samples were similar for both vegetarians and nonvegetarians</td>
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<tr>
<td>Not reported</td>
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<tr>
<td>n = 10 term infants and their mothers</td>
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<tr>
<td>Also examined preterm and very preterm infants</td>
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<td>Also measured GSHPx activity and protein content in milk</td>
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<th>Intake</th>
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<tbody>
<tr>
<td>Food scarcity</td>
<td></td>
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<tr>
<td>n = 55 Gambian women; multiparous</td>
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<tr>
<td>Food abundance</td>
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<tr>
<td>Milk Se was higher in the dry season</td>
<td></td>
</tr>
<tr>
<td>Food scarcity</td>
<td></td>
</tr>
<tr>
<td>Milk Se was lower in the rainy season, but only during early lactation (1–6 mo). The seasonal effect diminished during late lactation (13–19 mo)</td>
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</tr>
<tr>
<td>Food abundance</td>
<td></td>
</tr>
<tr>
<td>There was a negative correlation between parity and milk Se during late lactation regardless of season</td>
<td></td>
</tr>
<tr>
<td>Protein, GSHPx, and Px were not affected by state of lactation or parity</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intake</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informal dietary assessment</td>
<td></td>
</tr>
<tr>
<td>n = 20 Australian human milk-fed infants and their mothers, aged 17–38</td>
<td></td>
</tr>
<tr>
<td>Hind milk Se was significantly greater than fore milk Se</td>
<td></td>
</tr>
<tr>
<td>Blood and serum Se also measured</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intake</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>n = 50 German healthy term infants exclusively fed human milk</td>
<td></td>
</tr>
<tr>
<td>No change in plasma Se from birth to 4 mo</td>
<td></td>
</tr>
<tr>
<td>Significant decrease in erythrocyte and plasma GSHPx activity from birth to 4 mo</td>
<td></td>
</tr>
</tbody>
</table>

* Positive correlation between human milk selenium and GSHPx.

/ GSHPx = selenium-dependent glutathione peroxidases.

\[ \text{SEM} = \text{standard error of the mean.} \]
soil selenium content, with an overall average concentration of 18 µg (0.23 µmol)/L (Shearer and Hadjimarkos, 1975).

**Ages 0 through 6 Months**

There are no reports of full-term American or Canadian infants exclusively and freely fed human milk who manifest signs of selenium deficiency. The AI for infants ages 0 through 6 months is based on an average volume of milk intake for this age group of 0.78 L/day (Allen et al., 1991; Butte et al., 1984; Heinig et al., 1993) and an average concentration of selenium in human milk of 18 µg (0.23 µmol)/L (Levander et al., 1987; Mannan and Picciano, 1987; Shearer and Hadjimarkos, 1975; Smith et al., 1982). Using the average selenium concentration of milk of well-nourished but unsupplemented mothers, 18 µg (0.23 µmol)/L, the AI for infants 0 through 6 months of age would be 18 µg/L × 0.78 L/day = 14 µg/day, rounded up to 15 µg (0.19 µmol)/day.

**Ages 7 through 12 Months**

One method of estimating the AI for infants in the second half of the first year of life is to utilize the method described in Chapter 3 to extrapolate from the AI for infants ages 0 through 6 months and rounding. By this method, the AI for infants ages 7 through 12 months is 20 µg (0.25 µmol)/day.

An alternative method is to calculate the estimated selenium intake from human milk and infant foods. The selenium content of mature human milk remains relatively constant during the first year of lactation (Debski et al., 1989; Funk et al., 1990). Therefore, if 18 µg (0.23 µmol)/L selenium is the average human milk content in the United States and Canada (Shearer and Hadjimarkos, 1975) and 0.6 L/day is the usual amount of human milk consumed by infants 7 through 12 months of age (Dewey et al., 1984), the selenium intake from human milk would be 11 µg (0.14 µmol)/day.

The selenium content of the usual intakes of complementary weaning foods can be calculated as follows. The average daily caloric intake in this age group is 845 kcal (Fomon and Anderson, 1974). Calories provided by human milk would be 450 kcal (0.6 L of human milk × 0.75 kcal/mL) (Fomon and Anderson, 1974). Thus, the caloric content of the usual intake of complementary weaning foods would be 845 – 450 = 395 kcal.

There is one report in which the selenium content of infant food was analyzed. The total selenium intake of 20 apparently healthy
German infants and children 5 to 20 months old was reported to be 34 μg (0.4 μmol)/day; the median selenium content of the food was 27 ng (0.34 nmol)/g wet weight (Lombeck et al., 1984). By using this same selenium content for U.S. infant food and assuming an average of 1 kcal/g in infant foods, the average daily selenium intake from infant food in the second half of the first year of life would be 11 μg (0.027 μg/kcal × 395 kcal). Thus, 11 μg (0.14 μmol) from food + 11 μg (0.14 μmol) from human milk = 22 μg (0.28 μmol)/day. This is comparable to the value calculated above by extrapolating from the AI for infants 0 through 6 months, and is in the same range as the amount calculated by Levander (1976) of 28 μg (0.35 μmol)/day for a 6 month old consuming whole milk and weaning foods.

**Selenium AI Summary, Ages 0 through 12 Months**

**AI for Infants**

- 0–6 months: 15 μg (0.19 μmol)/day of selenium = 2.1 μg/kg
- 7–12 months: 20 μg (0.25 μmol)/day of selenium = 2.2 μg/kg

**Children and Adolescents Ages 1 through 18 Years**

**Evidence Considered in Estimating the Average Requirement**

No data were found on which to base an Estimated Average Requirement (EAR) for selenium for children or adolescents. In the absence of additional information, EARs and Recommended Dietary Allowances (RDAs) for children and adolescents have been estimated using the method described in Chapter 3, which extrapolates from adult values. As noted above, most selenium in the diet is metabolized by a mechanism similar to that of methionine. Therefore, the formulas used for determining selenium requirements for children are the metabolic formulas rather than those based upon weights alone. Given the reported slightly increased susceptibility of females to developing Keshan disease, selenium requirements for the various age groups are based on the higher reference weights for males.

The EAR is thus determined based on the same criteria of adequacy as adults, that of selenium intakes that would be expected to maximize plasma glutathione peroxidase activity.

It is important to discuss these recommendations in the context of knowledge regarding the amount of dietary selenium necessary to prevent Keshan disease. This disease occurs in young selenium-
deficient Chinese children, which suggests that these children have the greatest need for selenium of any individuals in the population. Studies in China indicate that Keshan disease does not occur in populations with a per capita adult selenium intake of 17 µg (0.22 µmol)/day or greater (Yang et al., 1987). Thus the calculated EARs listed below should be sufficient to prevent Keshan disease in all children.

### Selenium EAR and RDA Summary, Ages 1 through 18 Years

#### EAR for Children
- 1–3 years: 17 µg (0.22 µmol)/day of selenium
- 4–8 years: 23 µg (0.29 µmol)/day of selenium

#### EAR for Boys
- 9–13 years: 35 µg (0.45 µmol)/day of selenium
- 14–18 years: 45 µg (0.57 µmol)/day of selenium

#### EAR for Girls
- 9–13 years: 35 µg (0.45 µmol)/day of selenium
- 14–18 years: 45 µg (0.57 µmol)/day of selenium

The RDA for selenium is set by assuming a coefficient of variation (CV) of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement for selenium; the RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for selenium the RDA is 120 percent of the EAR). The calculated RDA is rounded to the nearest 5 µg.

#### RDA for Children
- 1–3 years: 20 µg (0.25 µmol)/day of selenium
- 4–8 years: 30 µg (0.38 µmol)/day of selenium

#### RDA for Boys
- 9–13 years: 40 µg (0.51 µmol)/day of selenium
- 14–18 years: 55 µg (0.70 µmol)/day of selenium

#### RDA for Girls
- 9–13 years: 40 µg (0.51 µmol)/day of selenium
- 14–18 years: 55 µg (0.70 µmol)/day of selenium

### Adults Ages 19 through 50 Years

**Evidence Considered in Estimating the Average Requirement**

Twenty years ago, efforts to estimate human selenium requirements could produce only an estimated safe and adequate daily
intake range that was based on extrapolations from experimentally
determined selenium requirements of animals (NRC, 1980b). Since
then, Keshan disease has been reported to be a disease of selenium
deficiency in humans, and estimates of the selenium intake needed
to prevent it have been made. Also, a number of selenoproteins,
many of them enzymes with important functions, have been identi-
fied. These selenoproteins require selenium for their synthesis and
for maintenance of their activities in tissues. As discussed earlier,
two plasma selenoproteins (glutathione peroxidase and selenopro-
tein P) can serve as indices of selenium status and have been mea-
sured in individuals consuming varying amounts of selenium.

Surveys in China have compared per capita daily selenium intakes
of adults in Keshan disease areas with intakes in adjacent areas that
were free of the disease (Yang and Xia, 1995; Yang et al., 1987).
Adult subjects living in the affected areas were found to have seleni-
um intakes of 11 µg (0.14 µmol)/day or less, while those living in
unaffected areas had intakes of 17 µg (0.22 µmol)/day or more.
Thus, based on one Chinese study, no selenium-responsive disease
is known to occur in populations with adult intakes as low as 17 µg
(0.22 µmol)/day.

Additional results from China and elsewhere indicate that intakes
of 20 µg (0.25 µmol)/day and greater protect adults against the
development of Keshan disease (Yang et al., 1987). In New Zealand
and Finland, intakes by adults as low as 25 µg (0.32 µmol)/day have
been reported without the occurrence of Keshan disease (Griffiths,
1973; Varo et al., 1994).

Plasma glutathione peroxidase and selenoprotein P were mea-
sured in a population in which Keshan disease was endemic (Hill et
al., 1996; Xia et al., 1989). Survey results estimated that per capita
selenium intake of adults was 11 µg (0.14 µmol)/day in this popula-
tion. Table 7-2 compares plasma selenium concentration, glu-
tathione peroxidase activity, and selenoprotein P concentrations in
boys aged 8 to 12 years and adult males residing in a Keshan disease
area with corresponding values in a nearby area free of the disease.
Males living in the disease-free area had been supplemented with
inorganic selenium for 14 days (100 µg [1.3 µmol]/day for the boys
and 200 µg [2.5 µmol]/day for the men). In the endemic area,
selenoprotein P concentration in boys and men was 13 percent and
23 percent, respectively, of that in the unaffected selenium supple-
mented area. Glutathione peroxidase activities were 26 percent in
the boys and 37 percent in the men, compared to these activities in
the boys and men in the unaffected area. Plasma selenium concen-
TABLE 7-2 Plasma Selenium Indices in Boys and Men in Two Areas of China: (1) A Selenium-Deficient Area Where Keshan Disease Was Endemic and (2) an Area Supplemented with Inorganic Selenium

<table>
<thead>
<tr>
<th></th>
<th>Plasmatic Selenium (µg/dL)</th>
<th>Plasma Glutathione Peroxidase (U/L&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>Plasma Selenoprotein P (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boys (aged 8–12)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-selenium area</td>
<td>1.3 ± 0.5</td>
<td>29 ± 15</td>
<td>0.10 ± 0.04</td>
</tr>
<tr>
<td>Supplemented area</td>
<td>6.3 ± 1.5</td>
<td>111 ± 21</td>
<td>0.76 ± 0.27</td>
</tr>
<tr>
<td>Low selenium/supplemented, %</td>
<td>21</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td><strong>Men (aged 17 and over)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-selenium area</td>
<td>1.6 ± 0.4</td>
<td>51 ± 16</td>
<td>0.13 ± 0.04</td>
</tr>
<tr>
<td>Supplemented area</td>
<td>6.8 ± 1.0</td>
<td>137 ± 15</td>
<td>0.57 ± 0.13</td>
</tr>
<tr>
<td>Low selenium/supplemented, %</td>
<td>24</td>
<td>37</td>
<td>23</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reference plasma contains 1 unit (U) selenoprotein P/L.

SOURCES: Hill et al. (1996); Xia et al. (1989).

These results show that biochemical functions of selenium are compromised in populations in which Keshan disease occurs. The results also show that development of the disease is possible in populations in which plasma glutathione peroxidase activities in adult males are as high as 37 percent of supplemented values. Finally, selenoprotein P concentrations appear to be more severely affected by selenium deficiency than is glutathione peroxidase activity.

Animal studies indicate that plasma selenoproteins reflect the activities of tissue selenoenzymes (Yang et al., 1989). It can therefore be argued that plateau concentrations of selenoenzymes in tissues would correlate with plateau concentrations of plasma selenoproteins. Xia et al. (1989) found that Keshan disease can occur in populations that have a plasma glutathione peroxidase activity in men that is 37 percent of maximum values. This would not leave a large margin of error if less than 100 percent of plasma glutathione peroxidase activity is deemed acceptable. For these two reasons, plateau concentration of plasma selenoproteins is chosen as the indicator for determining the selenium requirement.
**Intervention Studies**

Two intervention studies, one in China and one in New Zealand, have been done to assess the selenium intake required to achieve plateau concentrations of plasma selenoproteins.

**China Study.** In 1983, Yang et al. (1987) conducted an intervention study of selenium supplementation in China. Because the primary data from this study could not be obtained, interpretation of the results is based on a graph in the publication. The population consisted of men aged 18 to 42 years with dietary selenium intakes of 11 µg (0.14 µmol)/day and plasma glutathione peroxidase activities that were approximately 35 percent of the values reached after supplementation with the maximum amount of selenium. The men were studied in groups of eight to nine and were given selenium supplements of 0, 10, 30, 60, and 90 µg (0, 0.13, 0.38, 0.76, 1.14 µmol)/day as DL-selenomethionine for 8 months. Plasma glutathione peroxidase activities increased in all groups supplemented with selenium. The plasma enzyme activities in the groups given 30, 60, and 90 µg (0.38, 0.76, 1.14 µmol)/day increased and converged after the fourth month, whereas activities in the other two groups remained lower. This suggests that at a daily intake of 41 µg (0.52 µmol)/day of selenium (11 µg [0.14 µmol] from diet plus 30 µg [0.38 µmol] from supplement), the activity of plasma glutathione peroxidase reaches a plateau in adult Chinese males with an estimated weight of 60 kg. With a weight adjustment for North American males (41 µg (0.52 µmol)/day × 76 kg/60 kg), this value would translate to 52 µg (0.66 µmol)/day.

**New Zealand Study.** A study in New Zealand examined 52 adults (17 men and 35 women) aged 19 to 59 years with a mean selenium intake of 28 ± 15 µg (standard deviation [SD]) (0.35 ± 0.19 µmol)/day and initial plasma glutathione peroxidase activities that were approximately 75 percent of the values after selenium supplementation. The subjects were given 0, 10, 20, 30, or 40 µg (0, 0.13, 0.25, 0.38, 0.51 µmol)/day of selenium as selenomethionine for 20 weeks (with about 10 subjects per group) (Duffield et al., 1999).

An independent analysis of the study data (Duffield et al., 1999), which were generously provided by the investigators, has been conducted for this report. Regression analysis indicates that plasma glutathione peroxidase activities of the supplemented groups were higher than those of the placebo group, although the magnitude of the differences was small relative to the variation of values between indi-
individuals in the same supplemented group. Selenium supplementation increased the plasma glutathione peroxidase activity because the increase in the activity relative to presupplementation was apparent for nearly every supplemented individual. However, the increase at the lowest level tested (10 μg [0.13 μmol]/day) could not be statistically differentiated from the increase at the highest level tested (40 μg [0.51 μmol]/day). Thus, choosing to be conservative, an EAR of 38 μg (0.48 μmol) (28 μg [0.35 μmol]/day from food + 10 μg [0.13 μmol]/day from the lowest level supplemented) was selected.

**Summary.** Calculation of an EAR for selenium is based on the results of two intervention studies that were done in different countries but had similar designs. The Chinese study suggests that a plateau of plasma glutathione peroxidase activity was reached with a selenium intake of 41 μg (0.52 μmol)/day. With a weight adjustment for North American males, the selenium intake was 52 μg (0.66 μmol)/day. The New Zealand study can be interpreted to suggest an EAR in the vicinity of 38 μg (0.48 μmol)/day. The average of those studies, 45 μg (0.57 μmol), has been chosen as the EAR.

**Selenium EAR and RDA Summary, Ages 19 through 50 Years**

Based on the criterion of maximizing plasma glutathione peroxidase activity, the data described above support a selenium EAR of 45 μg/day for the age group 19 through 50 years based on the weights of North American men. Given the reported greater susceptibility of women to develop Keshan disease and the fact that the data used to set the EAR came largely from men, selenium requirements for both males and females are based on the higher reference weights for males.

**EAR for Men**
- 19–30 years: 45 μg (0.57 μmol)/day of selenium
- 31–50 years: 45 μg (0.57 μmol)/day of selenium

**EAR for Women**
- 19–30 years: 45 μg (0.57 μmol)/day of selenium
- 31–50 years: 45 μg (0.57 μmol)/day of selenium

The RDA for selenium is set by assuming a coefficient of variation (CV) of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement for selenium; the RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (there-
fore, for selenium the RDA is 120 percent of the EAR). The calculated RDA is rounded to the nearest 5 µg.

**RDA for Men**

- 19–30 years: 55 µg (0.70 µmol)/day of selenium
- 31–50 years: 55 µg (0.70 µmol)/day of selenium

**RDA for Women**

- 19–30 years: 55 µg (0.70 µmol)/day of selenium
- 31–50 years: 55 µg (0.70 µmol)/day of selenium

**Adults Ages 51 Years and Older**

Evidence Considered in Estimating the Average Requirement

Adults ages 51 years and older appear to have the same selenium requirement as younger adults. No pathological conditions related to selenium insufficiency have been reported in older individuals, and markers of selenium status in blood do not differ by age or gender (Hill et al., 1996).

**Selenium EAR and RDA Summary, Ages 51 Years and Older**

Data from intervention studies support an EAR for the age group 51 years and older of 45 µg/day. The aging process does not appear to impair selenium absorption or utilization.

**EAR for Men**

- 51–70 years: 45 µg (0.57 µmol)/day of selenium
- >70 years: 45 µg (0.57 µmol)/day of selenium

**EAR for Women**

- 51–70 years: 45 µg (0.57 µmol)/day of selenium
- >70 years: 45 µg (0.57 µmol)/day of selenium

The RDA for selenium is set by assuming a coefficient of variation (CV) of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement for selenium; the RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for selenium the RDA is 120 percent of the EAR). The calculated RDA is rounded to the nearest 5 µg.

**RDA for Men**

- 51–70 years: 55 µg (0.70 µmol)/day of selenium
- >70 years: 55 µg (0.70 µmol)/day of selenium
RDA for Women

51–70 years  55 µg (0.70 µmol)/day of selenium
>70 years  55 µg (0.70 µmol)/day of selenium

**Pregnancy**

*Evidence Considered in Estimating the Average Requirement*

Few studies provide information about 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 selenium content of 250 µg (3.2 µmol)/kg body weight (Schroeder et al., 1970), a 4-kg fetus would contain 1,000 µg (12.6 µmol) of selenium. This need could be met by an additional 4 µg (0.05 µmol)/day of selenium over the 270 days of the pregnancy. Based on this, an additional requirement of 4 µg (0.05 µmol)/day during pregnancy is estimated.

Reported selenium intakes of uncomplicated pregnancies have varied considerably. Levander et al. (1987) found that the average selenium intake of apparently healthy pregnant females in the United States was 73 µg (0.92 µmol)/day. Swanson et al. (1983) have shown that mean selenium retention in women fed a high-selenium diet (150 µg [1.9 µmol]/day) was 21 µg (0.27 µmol)/day in early pregnancy and 34 µg (0.43 µmol)/day in late pregnancy compared to 11 µg (0.14 µmol)/day for nonpregnant females. However, mean selenium intakes as low as 28 µg (0.35 µmol)/day have been reported for pregnant women in New Zealand without obvious ill effects for the newborn (Thomson and Robinson, 1980).

*Selenium EAR and RDA, Pregnancy*

Based on a fetal deposition of 4 µg (0.05 µmol)/day throughout pregnancy, the EAR is increased by 4 µg (0.05 µmol)/day during pregnancy. Since most selenium is highly bioavailable, no adjustment is made for absorption. No adjustment is made for the age of the mother.

**EAR for Pregnancy**

14–18 years  49 µg (0.62 µmol)/day of selenium
19–30 years  49 µg (0.62 µmol)/day of selenium
31–50 years  49 µg (0.62 µmol)/day of selenium

The RDA for selenium is set by assuming a coefficient of variation (CV) of 10 percent (see Chapter 1) because information is not avail-
able on the standard deviation of the requirement for selenium; the RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for selenium the RDA is 120 percent of the EAR). The calculated RDA is rounded to the nearest 5 µg.

**RDA for Pregnancy**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>RDA (µg) (µmol)/day of selenium</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–18 years</td>
<td>60 (0.76)</td>
</tr>
<tr>
<td>19–30 years</td>
<td>60 (0.76)</td>
</tr>
<tr>
<td>31–50 years</td>
<td>60 (0.76)</td>
</tr>
</tbody>
</table>

**Lactation**

_Evidence Considered in Estimating the Average Requirement_

As previously noted, human milk selenium concentration appears to be about 18 µg (0.23 µmol)/L in Canada and the United States (Levander et al., 1987; Mannan and Picciano, 1987; Shearer and Hadjimarkos, 1975; Smith et al., 1982). The average daily milk consumption in months 2 to 6 of lactation by infants is 0.78 L, so the average amount of selenium secreted in milk would be 14 µg (0.18 µmol)/day. Since most selenium in human milk is present as selenomethionine, which has a bioavailability greater than 90 percent (Thomson and Robinson, 1980), no adjustment is made for absorption. Therefore an increment of 14 µg (0.18 µmol)/day of selenium over the adult EAR is set for lactation.

Although the amount of selenium in human milk varies with the mother’s selenium intake, mean intakes as low as 4.7 µg (60 nmol)/day selenium in exclusively human milk-fed infants in Finland are not associated with selenium deficiency symptoms (Kumpulainen et al., 1983).

**Selenium EAR and RDA Summary, Lactation**

To estimate the EAR for lactation, 14 µg (0.18 µmol)/day of selenium is added to the EAR of 45 µg/day for the nonpregnant and nonlactating woman, giving an EAR of 59 µg (0.75 µmol)/day. No distinction is made for bioavailability or age of the mother.

**EAR for Lactation**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>EAR (µg) (µmol)/day of selenium</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–18 years</td>
<td>59 (0.75)</td>
</tr>
<tr>
<td>19–30 years</td>
<td>59 (0.75)</td>
</tr>
<tr>
<td>31–50 years</td>
<td>59 (0.75)</td>
</tr>
</tbody>
</table>
The RDA for selenium is set by assuming a coefficient of variation (CV) of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement for selenium; the RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for selenium the RDA is 120 percent of the EAR). The calculated RDA is rounded to the nearest 5 μg.

**RDA for Lactation**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>RDA for Selenium</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–18 years</td>
<td>70 μg (0.89 μmol)/day of selenium</td>
</tr>
<tr>
<td>19–30 years</td>
<td>70 μg (0.89 μmol)/day of selenium</td>
</tr>
<tr>
<td>31–50 years</td>
<td>70 μg (0.89 μmol)/day of selenium</td>
</tr>
</tbody>
</table>

### INTAKE OF SELENIUM

**Food Sources**

The selenium content of food varies depending on the selenium content of the soil where the animal was raised or the plant was grown: organ meats and seafood, 0.4 to 1.5 μg/g; muscle meats, 0.1 to 0.4 μg/g; cereals and grains, less than 0.1 to greater than 0.8 μg/g; dairy products, less than 0.1 to 0.3 μg/g; and fruits and vegetables, less than 0.1 μg/g (WHO, 1987). Thus the same foodstuffs may have more than a ten-fold difference in selenium content. Plants do not appear to require selenium and most selenium metabolism by plants occurs through sulfur pathways in which selenium substitutes for sulfur. Thus, plant content of selenium depends on the availability of the element in the soil where the plant was grown. This means that wheat grown in a low-selenium soil will have a low selenium content, whereas the same wheat variety grown in a high-selenium soil will have a high selenium content. For this reason, food tables that reflect average selenium contents are unreliable. Much plant selenium is in the form of selenomethionine, selenocysteine, or selenocysteine metabolites. Other organic forms of the element are known to exist, including some that have not yet been identified.

Unlike plants, animals require selenium. Meat and seafood are therefore reliable dietary sources of selenium. Meat and seafood contain selenium in its functional form as selenoproteins. Virtually all animal proteins contain selenomethionine obtained when the animal consumes selenium from plants. This means that meat varies in its selenium content depending largely on the selenomethionine intake of the animal.
Dietary Intake

Intake from Food

The dietary selenium intakes in the United States and Canada have been estimated in several studies. A detailed evaluation of diets consumed by 22 Maryland residents (using direct selenium analysis) indicated that selenium intake was $81 \pm 41$ (SD) $\mu$g ($1.0 \pm 0.5 \mu$mol)/day (Welsh et al., 1981). The Food and Drug Administration analyzed food items purchased in different regions of the United States over the period 1982 to 1991 and calculated dietary selenium intake from those results (Pennington and Schoen, 1996). The median calculated intake was 87 $\mu$g (1.1 $\mu$mol)/day with a range of 79 to 104 $\mu$g (1.0 to 1.3 $\mu$mol)/day in different years. These results support those of the Maryland study generally, but do not provide an indication of the extremes of selenium intake in the United States.

The Third National Health and Nutrition Examination Survey (NHANES III) intake data (Appendix Tables C-6 and C-7) reported higher median selenium intakes of 106 $\mu$g (1.3 $\mu$mol)/day from food and 108 $\mu$g (1.4 $\mu$mol)/day from food and supplements for all individuals based on dietary recall and food tables, but this method has low accuracy as discussed earlier. Selenium intake in Canada has been reported to be somewhat higher than U.S. intake, 113 to 220 $\mu$g (1.4 to 2.8 $\mu$mol)/day (Thompson et al., 1975).

Dietary intake of selenium varies tremendously among different populations. Factors that affect the intake include the geographic origin of the food items and the meat content of the diet. The lowest selenium intakes are in populations that eat vegetarian diets consisting of plants grown in low-selenium areas. Selenium-deficient Chinese populations live in low-selenium areas and are generally too poor to eat meat or to purchase food grown in other regions. Dietary intake of selenium in the United States and Canada varies by region but is buffered by the food distribution system. Thus, extensive transport of food throughout Canada and the United States prevents low-selenium geographic areas from having low dietary selenium intakes.

Intake from Water

Drinking water has been analyzed in the United States and several countries and does not supply nutritionally significant amounts of selenium (Bratakos et al., 1988; NRC, 1980a; Robberecht et al.,
Tap water is routinely used throughout the United States and Canada to raise selenium-deficient experimental animals. This is evidence that it contains very little selenium. In specific locales, however, water wells have been shown to supply much greater amounts of selenium. This is thought to result from irrigation practices, mining, or the presence of selenium-containing rocks (Valentine et al., 1978). Such high-selenium water supplies appear to be very limited and do not contribute to the selenium intake of large numbers of people (NRC, 1976).

Serum Concentrations

Information from NHANES III on serum selenium concentrations in a free-living population is given in Appendix Table F-3. Serum or plasma selenium concentrations greater than the 0.8 to 1.1 µmol/L (7 to 9 µg/dL) plateau concentration are associated with maximization of plasma selenoproteins (Hill et al., 1996). The NHANES III median serum selenium concentration was 1.4 µmol/L (12.4 µg/dL) for 17,630 subjects aged 9 to more than 70 years. The first percentile was 1.1 µmol/L (9.5 µg/dL) and the ninety-ninth percentile was 1.9 µmol/L (16.3 µg/dL). This shows that at least 99 percent of these subjects should have had maximal concentrations of plasma selenoproteins. Thus, the NHANES III serum data and dietary intake data (based on food tables) collected from 1988 to 1992 indicate that the selenium requirement of its participants was being met.

Intake from Supplements

In the United States or Canada, food is generally not fortified with selenium. An exception is proprietary infant formula that is designed to be the sole source of nutrients for the infant. Commercial formula manufacturers typically add selenium to ensure that infants consuming them will have an adequate selenium intake. Total selenium intakes from food plus supplements reported in NHANES III are found in Appendix Table C-7.

Selenium supplements of many strengths and types are available for purchase, and some popular multivitamin preparations contain selenium. However, according to NHANES III, selenium intake from both food (Appendix Table C-6) and food plus supplements (Appendix Table C-7) is above the EAR for most age groups in the United States. In the 1986 National Health Interview Survey, 9 per-
cent of all adults reported use of supplements containing selenium (Moss et al., 1989).

TOLERABLE UPPER INTAKE LEVELS

Hazard Identification

The Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals. Although members of the general population should be advised not to exceed the UL for selenium routinely, intake above the UL may be appropriate for investigation within well-controlled clinical trials. In light of evaluating possible benefits to health, clinical trials of doses above the UL should not be discouraged, as long as subjects participating in these trials have signed informed consent documents regarding possible toxicity and as long as these trials employ appropriate safety monitoring of trial subjects. Also, the UL is not meant to apply to individuals who are receiving selenium under medical supervision.

Adverse Effects

The Tolerable Upper Intake Level (UL) for selenium pertains to selenium intake from food and supplements. As discussed earlier, drinking water does not contain nutritionally significant amounts of selenium. The data on chronic selenosis, acute toxicity, and biochemical indicators of toxicity are reviewed.

Chronic Selenosis. Chronic toxicity of selenium has been studied in animals and has been observed in humans. The limited data available in humans suggest that chronic toxicities from inorganic and organic forms have similar clinical features but differ in rapidity of onset and relationship to tissue selenium concentrations. The most frequently reported features of selenosis (chronic toxicity) are hair and nail brittleness and loss (Yang et al., 1983). Other reported signs include gastrointestinal disturbances, skin rash, garlic breath odor (caused by selenium compounds), fatigue, irritability, and nervous system abnormalities (CDC, 1984; Helzlsouer et al., 1985; Jensen et al., 1984; Yang et al., 1983; G.-Q. Yang et al., 1989a).

The high prevalence of selenosis in Enshi, South China, provided an opportunity to study approximately 380 people with high selenium intakes (Yang and Zhou, 1994; G.-Q. Yang et al., 1989a, 1989b). Toxic effects occurred with increasing frequency in people with a
blood selenium concentration greater than 12.7 µmol/L (100 µg/dL), corresponding to a selenium intake above 850 µg/day.

**Acute Toxicity Effects.** There are a few reports in the literature of acute fatal or near-fatal selenium poisoning with either accidental or suicidal ingestion of selenium, usually in the form of gun blueing solution or sheep drench. Gun blue is a lubricant solution containing selenious acid, nitric acid, and copper nitrate (Ruta and Haidar, 1989). Ingestion of this liquid, which would result in ingestion of gram quantities of selenium, is typically followed by severe gastrointestinal and neurological disturbances, acute respiratory distress syndrome, myocardial infarction, and renal failure (Carter, 1966; Lombeck et al., 1987; Matoba et al., 1986; Nantel et al., 1985; Pentel et al., 1985). Autopsy revealed necrosis of gut and kidney, cardiomyopathy, and severe pulmonary edema.

**Biochemical Indicators of Selenium Toxicity.** Biochemical assessment of high selenium intakes is more difficult than assessment of low intakes. The selenoproteins are maximized when nutritional requirements of the element have been met and do not rise further with additional increments in selenium intake. Thus, measurement of selenoproteins is not useful in assessing potential toxicity.

Measurement of total selenium concentrations in tissue (including plasma and blood) is helpful in assessing the risk of toxicity from dietary selenium. Chinese investigators have correlated blood selenium concentrations with dietary intakes from high-selenium foodstuffs (Yang and Zhou, 1994).

High intakes of selenium in the form of selenomethionine, the major form of selenium in food, lead to large increases in tissue selenium concentrations. These increases are caused by the random incorporation of selenomethionine into proteins in place of methionine as discussed earlier. In contrast, inorganic forms of selenium, usually present in supplements, typically do not cause such high tissue concentrations because these forms of selenium cannot enter the methionine pool. However, inorganic selenium can cause toxicity at tissue levels of selenium much lower than seen with similar intakes of dietary selenium as selenomethionine. Severe toxicity was reported from selenite ingestion that increased blood concentrations by only a small amount (CDC, 1984). Thus, it is necessary to know the chemical form of selenium being ingested in order to use the tissue level of the element to estimate selenium intake due to release of selenium as a result of normal protein metabolism.
Incorporation of dietary selenomethionine into protein delays selenium toxicity. This storage has created the impression that protein-bound dietary selenium is less toxic than inorganic selenium. Although inorganic selenium has greater immediate toxicity than does selenomethionine, both forms are likely to have similar toxicities under conditions of chronic intake.

Methylated selenium metabolites appear in the breath when large quantities of the element are ingested (McConnell and Portman, 1952). These metabolites are responsible for a garlic odor of the breath. Measurement of excretory metabolites of selenium, whether urinary or breath, is subject to significant error, because excretion by these routes is a function of recent intake as well as long-term selenium status. For example, selenium-deficient rats given a single large dose of selenium excrete part of that dose in the breath (Burk et al., 1972). In addition, quantitation of breath selenium excretion has never been linked to selenium toxicity. Based on these considerations, breath selenium cannot be used as an index of selenium toxicity at present, and urinary selenium excretion can be used as an index of toxicity only under carefully controlled conditions.

Summary

Based on considerations of causality, relevance, and the quality and completeness of the database, hair and nail brittleness and loss were selected as the critical endpoints on which to base a UL. Hair and nail brittleness and loss have been reported more frequently than other signs and symptoms of chronic selenosis. Biochemical markers have too much variation to be reliable except under controlled conditions.

Dose-Response Assessment

Adults

Data Selection. A useful data set for determining dose-response of selenium toxicity from food sources was reported by Chinese investigators (Yang and Zhou, 1994). That report consisted of a reexamination (in 1992) of five patients previously found (in 1986) to have overt signs of selenosis: hair loss and nail sloughing. Because the same patients were studied at different times while consuming the same food form of selenium, blood levels of selenium can be compared and dietary intakes can be inferred from blood selenium concentrations.
Identification of a No-Observed-Adverse-Effect Level (NOAEL) and a Lowest-Observed-Adverse-Effects Level (LOAEL). The lowest blood level of selenium measured in the five subjects at initial examination was 13.3 μmol/L (105 μg/dL), corresponding to a selenium intake of 913 μg (12 μmol)/day (range: 913 to 1,907 μg [12 to 24 μmol]/day). The average blood selenium level was 16.9 μmol/L (135 μg/dL). At the time of reexamination in 1992, all five patients were described as recovered from selenium poisoning, although their fingernails reportedly appeared brittle. The mean blood selenium level had decreased to 12.3 μmol/L (97 μg/dL), corresponding to a selenium intake of about 800 μg (10 μmol)/day (range 654 to 952 μg [8.3 to 12 μmol]/day). The lower limit of the 95 percent confidence interval was 600 μg (7.6 μmol)/day.

Yang and Zhou (1994) therefore suggested that 913 μg (12 μmol)/day of selenium intake represents an individual marginal toxic daily selenium intake or LOAEL. They further suggested that the mean selenium intake upon reexamination (800 μg [10 μmol]/day), represented a NOAEL, while 600 μg (7.6 μmol)/day of selenium intake was the lower 95 percent confidence limit for the NOAEL. These values appear reasonable, although the number of subjects was small. Nevertheless, the LOAEL for selenosis in this small data set appears to be representative of the larger data set, and the reexamination of the subjects provides valuable dose-response data. Uncertainty occurs because of the smallness of the data set and because the Chinese subjects may not be typical (e.g., they may be more or less sensitive to selenium than other populations).

Longnecker et al. (1991) studied 142 ranchers, both men and women, from eastern Wyoming and western South Dakota who were recruited to participate and were suspected of having high selenium intakes based on the occurrence of selenosis in livestock raised in that region. Average selenium intake was 239 μg (3 μmol)/day. Dietary intake and selenium in body tissues (whole blood, serum, urine, toenails) were highly correlated. Blood selenium concentrations in this western U.S. population were related to selenium intake in a similar manner to that found in the Chinese studies, presumably because the form of selenium ingested was selenomethionine. No evidence of selenosis was reported, nor were there any alterations in enzyme activities, prothrombin times, or hematology that could be attributed to selenium intake. The highest selenium intake in the study was 724 μg (9 μmol)/day.

It thus appears that a UL based on the Chinese studies is protective for the population in the United States and Canada. Therefore a NOAEL of 800 μg (10 μmol)/day is selected.
Uncertainty Assessment. An uncertainty factor (UF) of 2 was selected to protect sensitive individuals. The toxic effect is not severe, but may not be readily reversible, so a UF greater than 1 is needed.

Derivation of a UL. The NOAEL of 800 µg/day was divided by a UF of 2 to obtain a UL for adults as follows:

\[
\frac{\text{NOAEL}}{\text{UF}} = \frac{800 \mu g/\text{day}}{2} = 400 \mu g/\text{day}.
\]

Selenium UL Summary, Ages 19 Years and Older

UL for Adults

- 19 years and older: 400 µg (5.1 µmol)/day of selenium

Pregnancy and Lactation

Brätter et al. (1996) studied the effects of selenium intake on metabolism of thyroid hormones in lactating mothers in seleniferous regions in the foothills of the Venezuelan Andes. Selenium intakes ranged from 170 to 980 µg (2.2 to 12.4 µmol)/day. An inverse correlation between selenium intake and free triiodothyronine (FT₃) was observed, but all values were found to be within the normal range.

There are no reports of teratogenicity or selenosis in infants born to mothers with high but not toxic intakes of selenium. Therefore, ULs for pregnant and lactating women are the same as for nonpregnant and nonlactating women (400 µg [5.1 µmol]/day).

Selenium UL Summary, Pregnancy and Lactation

UL for Pregnancy

- 14–18 years: 400 µg (5.1 µmol)/day of selenium
- 19 years and older: 400 µg (5.1 µmol)/day of selenium

UL for Lactation

- 14–18 years: 400 µg (5.1 µmol)/day of selenium
- 19 years and older: 400 µg (5.1 µmol)/day of selenium

Infants and Children

Data Selection. There are several approaches for estimating a UL in human milk-fed infants (Levander, 1989). However, the most conservative approach is to use the data of Shearer and Hadjimarkos (1975).
Identification of a NOAEL. The data of Shearer and Hadjimarkos (1975) showed that a human milk selenium concentration of 60 µg (0.8 µmol)/L was not associated with known adverse effects. Thus, 60 µg (0.8 µmol)/L is the NOAEL selected. Multiplying the NOAEL for infants 0 through 6 months of age by the estimated average intake of human milk of 0.78 L/day results in a NOAEL of 47 µg (0.6 µmol) or approximately 7 µg (90 nmol)/kg/day. This is in agreement with another study by Brätter et al. (1991).

Brätter et al. (1991) studied effects of selenium intake on children in two seleniferous areas of the foothills of the Venezuelan Andes, using Caracas as a control. Mean human milk selenium content was 46 µg (0.6 µmol)/L in Caracas compared to 60 and 90 µg (0.8 and 1.1 µmol)/L in the two seleniferous areas. Mean selenium concentrations in infant blood in the area with the highest adult selenium intake were reported to be intermediate between those seen in the seleniferous and the non-seleniferous regions.

Uncertainty Assessment. There is no evidence that maternal intake associated with a human milk level of 60 µg (0.8 µmol)/L results in infant or maternal toxicity (Shearer and Hadjimarkos, 1975). Therefore, a UF of 1 is specified.

Derivation of a UL. The NOAEL of 47 µg (0.6 µmol)/day was divided by a UF of 1, resulting in a UL of 47 µg (0.6 µmol) or approximately 7 µg (90 nmol)/kg/day for 2 through 6-month-old infants. Thus, the infant UL and the adult UL are similar on a body weight basis. Also, there is no evidence indicating increased sensitivity to selenium toxicity for any age group. Thus, the UL of 7 µg/kg body weight/day was adjusted for older infants, children, and adolescents on the basis of relative body weight as described in Chapter 4 using reference weights from Chapter 1 (Table 1-1). Values have been rounded down to the nearest 5 µg.

Selenium UL Summary, Ages 0 Months through 18 Years

<table>
<thead>
<tr>
<th></th>
<th>UL for Infants</th>
<th>UL for Children</th>
<th>UL for Adolescents</th>
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<tbody>
<tr>
<td>0–6 months</td>
<td>45 µg (0.57 µmol)/day of selenium</td>
<td>90 µg (1.1 µmol)/day of selenium</td>
<td>400 µg (5.1 µmol)/day of selenium</td>
</tr>
<tr>
<td>7–12 months</td>
<td>60 µg (0.76 µmol)/day of selenium</td>
<td>150 µg (1.9 µmol)/day of selenium</td>
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<tr>
<td>1–3 years</td>
<td></td>
<td>280 µg (3.6 µmol)/day of selenium</td>
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<tr>
<td>4–8 years</td>
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<td></td>
<td></td>
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<tr>
<td>9–13 years</td>
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<td></td>
<td></td>
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<tr>
<td>14–18 years</td>
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</table>
Intake Assessment

Selenium intake is primarily in the form of food. Reliance on foods grown in high-selenium areas causes selenosis in China (Yang et al., 1983). There are high-selenium areas in the United States, but the U.S. Department of Agriculture has identified them and proscribed their use for raising animals for food. The extensive food distribution system in Canada and the United States ensures that individuals do not eat diets that originate solely from one locality. This moderates the selenium content of diets, even in high-selenium areas.

The study of dietary selenium intake in a high-selenium area (western South Dakota and eastern Wyoming) indicated daily intakes of 68 to 724 µg (0.9 to 9.2 µmol) in 142 subjects (Longnecker et al., 1991). About half the subjects were consuming more than 200 µg (2.5 µmol)/day. No evidence of selenosis was found, even in the subjects consuming the most selenium.

Water selenium content is usually trivial compared to food selenium content. However, irrigation runoff water has been shown to contain significant amounts of selenium when the soil irrigated contains large amounts of the element (Valentine et al., 1978).

Selenium is available over the counter in many doses but usually under 100 µg (1.3 µmol)/dose. Some individuals may consume larger quantities than are recommended by the manufacturer. At least one manufacturing error has been reported to have led to selenium intoxication in 13 people who took a selenium supplement containing 27.3 mg, several hundred times the amount of selenium stated to be in the product (Helzlsouer et al., 1985).

Risk Characterization

The risk of selenium intake above the UL for the U.S. and Canadian populations appears to be small. There is no known seleniferous area in the United States and Canada where there have been recognized cases of selenosis. Specifically as noted above, there have been no cases of selenosis in the high-selenium areas of Wyoming and South Dakota (Longnecker et al., 1991). There is some potential for selenium intake to exceed the UL in this area. These authors note that selenium intake exceeded 400 µg (5.1 µmol)/day in 12 subjects, with the highest intake being 724 µg (9.2 µmol)/day. Since 724 µg (9.2 µmol)/day is 3.4 standard deviations above the mean intake, intakes this high would be very rare. Even at this level, toxic effects would be unlike-
ly, since the LOAEL is about 900 µg (11.4 µmol)/day, and many people would not be affected even at this level of intake.

Although intakes above the UL indicate an increased level of risk, these intakes—if below the LOAEL—would nevertheless be unlikely to result in observable clinical disease. This is especially true in a population that could self-select for high intake, so that people who might experience symptoms could alter their diets or move. In light of evaluating possible benefits to health, clinical trials at doses of selenium above the UL should not be discouraged, as long as subjects participating in these trials have signed informed consent documents regarding possible toxicity and as long as these trials employ appropriate safety monitoring of trial subjects. Also, the UL is not meant to apply to individuals who are receiving selenium under medical supervision.

RESEARCH RECOMMENDATIONS FOR SELENIUM

• Biomarkers for use in assessment of selenium status are needed to prevent selenium deficiency and selenium toxicity. The relationship of plasma selenoprotein concentrations to graded selenium intakes must be studied in a severely selenium-deficient population in order to establish a more precise dietary selenium requirement. Plasma selenium levels (and other measurements of the element) have to be carried out in subjects fed levels of selenium (both organic and inorganic forms) up to the Tolerable Upper Intake Level (UL). This could validate use of plasma selenium concentrations to assess high levels of selenium intake.

• Since the Recommended Dietary Allowances (RDAs) for children ages 1 through 18 years are extrapolated from the adult RDAs, it is critically important to conduct large-scale studies with children using state-of-the-art biomarkers to assess their selenium requirements.

• Selenium functions largely through selenoproteins. Although the functions of some selenoproteins are known, those of others are not. Moreover, there appear to be a number of selenoproteins that have not yet been characterized. Therefore, the functions of known and new selenoproteins need to be determined.

• At present the recommendation for selenium intake has been set at the amount needed to achieve a plateau of the plasma selenoprotein glutathione peroxidase. Most residents in Canada and the United States can reach this level of selenium intake with their usual diet, but residents of many regions of the world have lower selenium intakes. Research is needed to determine the health conse-
quences of selenium intakes inadequate to allow full selenoprotein expression.

- Limited evidence has been presented that intakes of selenium greater than the amount needed to allow full expression of selenoproteins may have chemopreventive effects against cancer. Controlled intervention studies are needed to fully evaluate selenium as a cancer chemopreventive agent.

REFERENCES


