(2) Microminerals

Iron

1. Background Information

1─1. Definition and Classification

Iron is a transition metal element (atomic number: 26, Fe). It is predominantly stored as heme iron which is found in combination with protein, as well as non-heme iron: which is inorganic in food.

2. To Avoid Inadequacy

2─1. Method Used to Set the Estimated Average Requirements (EAR) and Recommended Dietary Allowances (RDA)

The EAR for iron can be calculated using balance tests and factorial modeling methods, except in the case of infants aged 0-5 months. However, the iron balance in the body can be maintained at low iron intakes, and, as the rate of iron absorption changes depending on dietary intake, the requirement may be underestimated when the results of balance tests are used. Therefore, the EAR was determined using a factorial modeling method. Although a number of studies used factorial modeling methods, few of those studies were conducted in Japanese settings. For those aged over 6 months, the principal calculation methods are based on the US-Canada DRIs(1), using body weight (BW) and menstrual blood loss values from Japanese studies. For infants, the adequate intake (AI) was determined using the iron concentration in breast milk, and the average milk volume (0.78 L/day)(2,3).

2─1─1. Factors Used in the Factorial Modeling Method

2─1─1─1. Basal Iron Loss

The basal iron loss measured in 41 people from 4 groups (mean BW 68.6 kg) was 0.9-1.0 mg/ day (mean 0.96 mg/day), and the difference between the groups was relatively small(4); these findings are similar to those of a recent study(5). This value was extrapolated to each sex and age group, using the 0.75th power of the BW ratio (Table 1).

Table 1. Estimation of basal iron loss

Age	Male				Female			
	Intermediate age (year)	Reference BW (kg)	BW increase (kg/year)[1]	Basal iron loss (mg/day)[2]	Intermediate age (year)	Reference BW (kg)	BW increase (kg/year)[1]	Basal iron loss (mg/day)[2]
6-11 (months)	0.75	8.8	3.6	0.21	0.75	8.1	3.4	0.19
1-2 (years)	2.0	11.5	2.1	0.25	2.0	11.0	2.2	0.24
3-5 (years)	4.5	16.5	2.1	0.33	4.5	16.1	2.2	0.32
6-7 (years)	7.0	22.2	2.6	0.41	7.0	21.9	2.5	0.41
8-9 (years)	9.0	28.0	3.4	0.49	9.0	27.4	3.6	0.48
10-11 (years)	11.0	35.6	4.6	0.59	11.0	36.3	4.5	0.60
12-14 (years)	13.5	49.0	4.5	0.75	13.5	47.5	3.0	0.73
15-17 (years)	16.5	59.7	2.0	0.86	16.5	51.9	0.6	0.78
18-29 (years)	24.0	63.2	0.4	0.90	24.0	50.0	0.0	0.76
30-49 (years)	40.0	68.5	0.1	0.96	40.0	53.1	0.1	0.79
50-69 (years)	60.0	65.3	-	0.93	60.0	53.0	-	0.79
70 years+	-	60.0	-	0.87	-	49.5	-	0.75

[1] Calculated using values of the reference BW

[2] Extrapolated using a value of basal iron loss (0.96mg/day, BW 68.6kg) and the 0.75th power of the BW ratio

2─1─1─2. Iron Storage for Growth

Iron is stored according to growth requirements during childhood. The iron storage with growth respect to growth requirements can be stratified into a) iron content in hemoglobin, b) increase in tissue iron (non-storage iron), and c) increase in storage iron.

(1) Iron storage in hemoglobin

The iron storage with growth for each sex and age group was estimated using the following formulas that were employed in the US-Canada DRIs(1).

【6-11 months old】 Iron storage in hemoglobin (mg/day) = BW increase (kg/year) × blood volume [70 mL/kg]× hemoglobin concentration [0.12 g/mL] × iron content in hemoglobin [3.39 mg/g]÷ 365 days

【1-9 years old】 Iron storage in hemoglobin (mg/day) = (blood hemoglobin level of one level upper age class (g) – blood hemoglobin level at the target age class (g)) × iron content in hemoglobin [3.39 mg/g] ÷ (the middle age of one level upper age class – the middle age of the target age class) ÷ 365 days

【10-17 years old】 Iron storage in hemoglobin (mg/day) = (reference BW (kg) × increase in hemoglobin concentration (g/L/year)＋BW increase (kg/year)× hemoglobin concentration (g/L)) × blood volume [0.075 L/kg] × iron content in hemoglobin [3.39 mg/g] ÷ 365 days

For those aged 1-9 years, the blood volume for each age and sex group was calculated using a regression equation estimated employing the values for those aged 1-11 years(6): (boys: 0.0753 × BW (kg)－0.05, girls: 0.0753×BW (kg) + 0.01). Blood hemoglobin concentrations were estimated using a regression equation with age and hemoglobin concentration, as determined in a Canadian study(7). The iron content in hemoglobin was determined as 3.39 mg/g(8).

（2）Increase in tissue iron (non-storage iron) level

The increase in the tissue iron (non-storage iron) level was calculated using the following formula:

Tissue iron per BW (0.7 mg/kg) × increase in BW (kg/year) ÷ 365 days

（3）Increase in storage iron level

The increase in the storage iron level was reported to be 12% of the total iron storage in children aged 1-2 years(9). Considering this, for children aged 6 months to 2 years, the increase in the storage iron level was estimated to be 12% of the increase in the total iron storage for growth, including the factors mentioned above ((1) and (2)). This percentage was assumed to decrease linearly after age 3 years, and reach 0 at 9 years of age(9). Table 2 shows the increase in the storage iron for each age and sex group.

Table 2. Estimation of the increase in the storage iron (6 months to 17 years old)

Gender	Age	Blood volume (L)[1]	Hemoglobin concentration (g/L)[2]	Increase in hemoglobin concentration (g/L/year)[2]	Blood hemoglobin (g)[3]	Iron storage in hemoglobin (mg/day)[4]	Non-storage iron increase (mg/day)[5]	Storage iron increase (mg/day)[6]	Total iron storage (mg/day)
Male	6-11 (months)	-	-	-	-	0.28	0.01	0.04	0.33
	1-2 (years)	0.82	121.8	-	99.4	0.19	0.00	0.02	0.21
	3-5 (years)	1.19	125.3	-	149.4	0.22	0.00	0.02	0.24
	6-7 (years)	1.62	128.8	-	208.9	0.29	0.00	0.01	0.30
	8-9 (years)	2.06	131.6	-	270.9	0.38	0.01	0.00	0.39
	10-11 (years)	2.63	134.4	1.40	353.6	0.46	0.01	-	0.47
	12-14 (years)	-	137.9	1.40	-	0.48	0.01	-	0.49
	15-17 (years)	-	150.4	3.40	-	0.35	0.00	-	0.36
Female	6-11 (months)	-	-	-	-	0.26	0.01	0.04	0.31
	1-2 (years)	0.84	123.2	-	103.3	0.19	0.00	0.03	0.22
	3-5 (years)	1.22	126.0	-	154.0	0.22	0.00	0.02	0.25
	6-7 (years)	1.66	128.7	-	213.5	0.27	0.00	0.01	0.28
	8-9 (years)	2.07	130.9	-	271.4	0.44	0.01	0.00	0.44
	10-11 (years)	2.74	133.1	1.10	365.1	0.44	0.01	-	0.45
	12-14 (years)	-	135.9	1.10	-	0.32	0.01	-	0.32
	15-17 (years)	-	135.6	0.28	-	0.07	0.00	-	0.07

[1] Estimated using regression formulas (male: 0.0753×BW-0.05, female: 0.0753×BW+0.01), according to the report by Hawkins(6)

[2] Estimated using a formula of association between age and hemoglobin concentration(7)

[3] Blood hemoglobin (g) = blood volume (L) × hemoglobin concentration (g/L)

[4] 6-11 months old: Iron storage in hemoglobin (mg/day) = BW increase (kg/year) × blood volume [70 mL/kg]× hemoglobin concentration [0.12 g/mL]× iron content in hemoglobin [3.39 mg/g(8)] / 365 days

1-9 years old: Iron storage in hemoglobin (mg/day) = (blood hemoglobin level of one level upper age class (g) – blood hemoglobin level at the target age class (g)) × iron content in hemoglobin [3.39 mg/g] / (the middle age of one level upper age class – the middle age of the target age class) / 365 days

10-17 years old: Iron storage in hemoglobin (mg/day) = (reference BW (kg) × increase in hemoglobin concentration (g/L/year) ＋BW increase (kg/year)× hemoglobin concentration (g/L)) × blood volume [0.075 L/kg]× iron content in hemoglobin [3.39 mg/g]/ 365 days

[5] Non-storage iron increase (mg/day) = BW increase (kg/year) × storage iron per BW [0.7 mg/kg] / 365 day

[6] Estimated as 12% of total iron storage for 6 months to 2 years old, with decreasing after 3 years old to 0 at 9 years old(9).

2─1─1─3. Menstrual Iron Loss

Menstrual iron loss is strongly associated with iron deficiency anemia(10). According to a review of several studies that examined Japanese women aged around 20 years, the geometric mean menstrual blood loss was 37.0 mL/period, and the median duration of the menstrual cycle was 31 days(11); this finding was supported by a recent study(12). However, age-related variations in menstrual blood loss have not been reported in Japanese women aged over 20 years. A Japanese study of high school female students reported that the geometric mean menstrual blood loss was 31.1 mL/period, and the median duration of the menstrual cycle was 31 days(13). From these results, the menstrual blood loss was determined to be 37 mL/period for those aged over 18 years and 31.1 mL/period for those aged 10-17 years, and the duration of the menstrual cycle was determined to be 31 days for all age groups, for the calculation of menstrual iron loss. Using a hemoglobin concentration of 135 g/L(14), and hemoglobin iron content of 3.39 mg/g for all age groups, the requirement values for the compensation of the menstrual loss were estimated to be 3.06 mg/ day for those aged 10-17 years, and 3.64 mg/day for those aged 18 years or older.

Table 3. Estimation of dietary iron requirement for compensation of the menstrual loss (women)

Subjects	Menstrual blood volume (mL/times)	Menstrual cycle (day)	Iron loss (mg/day)[1]	Required intake to compensate the iron loss(mg/day)[2]
10-17(years)	31.1	31	0.46	3.06
18 years +	37.0	31	0.55	3.64

[1] Iron loss (mg/day) = menstrual blood volume (mL)/Japanese menstrual cycle [31 days](13) × hemoglobin concentration [0.135g/mL](14) × iron concentration in hemoglobin [3.39mg/g]

[2] Iron intake (mg/day) = iron loss (mg/day) / absorption rate [0.15]

Adult menstrual blood loss displays an almost-log-normal distribution. A study reported that the 95th percentile value of the loss was 115 mL/period for women without iron deficiency anemia(15), while another study reported that 85% of women lose less than 120 mL/period(16). Although these values are much higher than those used in the definition of hypermenorrhea (>80 mL/period)(17), few relevant studies have been conducted in Japanese populations. Therefore, the EAR and RDA were determined for people without hypermenorrhea, whose menstrual blood loss is less than 80 mL/period. When excluding those with hypermenorrhea, the distribution of adult menstrual blood loss was relatively close to normal, and the mean value of menstrual blood loss could be estimated to be lower than when hypermenorrhea is included. However, since these data remained unclear, the DRIs used the geometric mean menstrual blood loss including hypermenorrhea (over 20 years old: 37.0 mL/period, 10-17 years old: 31.1 mL/period) for the calculation of the EAR and RDA.

2─1─1─4. Dietary Iron Absorption Rate

The dietary iron absorption rate is reported to be 16.6% from the normal American diet, 16% from the normal French diet, and 14% from the normal Swedish diet(14). The rate varies based on multiple factors such as the dietary composition ratio of heme iron and non-heme iron, the intake of nutrients and food that promote or inhibit iron absorption, and the need for iron, making it difficult to determine a representative value for the dietary iron absorption rate. In the present DRIs, the dietary iron absorption rate was estimated to be 15% for all age and sex groups, except for infants, in accordance with a value adopted by the WHO and the Food and Agricultural Organization (FAO)(17) (15%).

The absorption rate of iron, especially inorganic iron, increases when there is a need for iron. Among Japanese people, inorganic iron intake comprises a majority of the dietary iron intake, due to their high intake of plant foods. Therefore, the absorption rate from the Japanese diet may be higher than 15%; however, this elevated absorption may be derived from low iron intake. Therefore, the iron absorption rate was determined to be 15%, as its use was considered appropriate under conditions of sufficient intake.

2─1─1─5. Interindividual Difference of Requirement

In the US-Canada DRIs(1), the coefficient of variation for interindividual requirement was determined to be 40% for children aged 8 years or younger, 20% for those aged 11 years, and 10% for those aged 16 years, based on the variance in the increase in body surface area and BW. Few relevant reports have focused on young children; therefore, the coefficient of variation for iron was determined to be 20% for children aged 6 months-14 years, and 10% for those aged over 15 years.

2─1─2. Adults (EAR, RDA)

2─1─2─1. Men and Non-menstruating Women

The EAR was calculated as follows: EAR = basal iron loss (Table 1) ÷ absorption rate (0.15). The RDA was determined as the EAR × 1.2, using 10% as the coefficient of variation.

2─1─2─2. Menstruating Women

The EAR was calculated as follows: EAR = [basal iron loss (Table 1) + menstrual iron loss (0.55 mg/day (Table 3)] ÷ absorption rate (0.15). The RDA was determined as the EAR × 1.2, using 10% as the coefficient of variation. These values were set for those without hypermenorrhea (>80 mL/period). For those with hypermenorrhea, the EAR and RDA were estimated to be more than 13 mg/day and 16 mg/day, respectively. It is difficult to achieve the dietary iron intakes reported in the National Health and Nutrition Survey through typical foods, and iron supplementation under medical supervision is required.

2─1─3. Children (EAR, RDA)

2─1─3─1. Boys and Non-Menstruating Girls

The EAR was calculated as follows: EAR = [basal iron loss (Table 1) + iron storage in hemoglobin (Table 2) + increase in tissue iron (non-storage iron) level (Table 2) + increase in storage iron level (Table 2)] ÷ absorption rate (0.15). The RDA was determined as the EAR × 1.4 for those aged 1–14 years, and EAR × 1.2 for those aged 15 years or older.

2─1─3─2. Menstruating Girls

For girls aged 10 years or older, the EAR was calculated considering the menstrual iron loss as follows: EAR = [basal iron loss (Table 1) + iron storage in hemoglobin (Table 2) + increase in tissue iron (non-storage iron) level (Table 2) + increase in storage iron level (Table 2) + menstrual iron loss (0.46 mg/day) (Table 3)] ÷ absorption rate (0.15). The RDA was determined as the EAR × 1.4 for those aged 1–14 years, and EAR × 1.2 for those aged 15 years or older. These values were set for those without hypermenorrhea (>80 mL/period).

2─1─4. Infants

2─1─4─1. 0-5 months old (AI)

Fetal hemoglobin is degraded after birth, and iron is released; thereafter, the adult hemoglobin begins its biosynthesis. Accordingly, the blood hemoglobin concentration reaches a minimum level during the 4-6 months after birth, and increases thereafter. As full-term newborns with normal intrauterine growth, weighing more than 3 kg, can maintain normal iron metabolism by utilizing the body iron storage during the first 4 months of life, iron deficiency anemia develops more frequently during the later stages of infancy (such as the weaning period)(18). The AI was estimated by multiplying the iron concentration in the breast milk of Japanese women (0.426 mg/L)(19), and the average milk intake (0.78 L/day)(2,3), as the iron intake from breast milk was considered sufficient for infants aged 0-5 months. The AI was determined as 9.5 mg /day by rounding 0.332 mg/day.

Although there is no apparent difference between the growth of breast milk-fed infants and non-breast milk-fed infants, breast milk-fed infants were reported to have a lower hemoglobin concentration and anemic tendency(20). Iron supplementation using infant formula needs to be considered when needed, among exclusively breast milk-fed infants with iron deficiency anemia, as breast milk may not provide sufficient iron.

2─1─4─2. 6-11 months old (EAR, RDA)

Lower hemoglobin concentrations have been reported among 6-month-old breast milk-fed Japanese infants. Therefore, the value extrapolated from the AI for children aged 0-5 months can be lower for the prevention of iron deficiency. Therefore, the EAR for children aged 6-11 months was determined using the same calculation as that used in other children as follows: EAR = [basal iron loss (Table 1) + iron storage in hemoglobin (Table 2) + increase in tissue iron (non-storage iron) level (Table 2) + increase in storage iron level (Table 2)] ÷ absorption rate (0.15). The RDA was determined as the EAR × 1.4, using 20% as the coefficient of variation.

2─1─5. Additional Amount for Pregnant Women (EAR, RDA)

In addition to basal iron loss, fetal iron storage, placental iron storage, and an increase in the hemoglobin mass caused by erythrocyte mass expansion are required during pregnancy. Each of the above-stated factors varies by the pregnancy stage.

For the DRIs, the values shown in Table 4 were used for fetal and placental iron storage(21). The values for the increase in the hemoglobin mass caused by erythrocyte mass expansion were calculated based on the reference weight (age 18-29 years, 50.6 kg), blood volume (0.075 L/kg BW), increase in blood volume during pregnancy (30-50%), hemoglobin concentration standard for pregnant women (110 g/L: criteria for pregnancy anemia), hemoglobin concentration for adult women (135 g/L)(18), and iron content in hemoglobin (3.39 mg/g)(8). Using a BW of 50.6 kg for non-pregnant women, the hemoglobin iron content was estimated to be 1,737 mg (50.6 × 0.075 × 135 × 3.39＝1,737 mg), and the minimum estimate for the iron content in hemoglobin at the time of delivery, in the absence of pregnancy anemia, was estimated to be 1,840-2,123 mg (50.6 × 0.075 × 1.3 - 1.5 × 110 × 3.39＝1,840-2,123 mg). The difference between these values was 103-386 mg; therefore, the total usage of iron throughout pregnancy was estimated to be approximately 300 mg. Furthermore, this demand expands greatly during the second and third trimesters, with an equal division between the terms.

With these estimates, the additional iron requirements for pregnant women were calculated to be 0.32 mg/day, 2.68 mg/day and 3.64 mg/day, in the early, mid, and late stages, respectively. Using a dietary iron absorption rate of 15% in the early stage, and 25% in the second and late stages, the dietary iron requirements were calculated to be 2.1 mg/day, 10.7 mg/day, and 14.6 mg/day for early-, mid- and late-stage pregnancies, respectively. The average value for the mid and late stages was calculated, and this was adopted for the EAR for these two terms. Thus, the additional EAR was determined to be 2.0 mg/day for the early stage, and 12.5 mg/day for the mid and late stages, after rounding. The additional RDA was determined as the EAR × 1.2, using 10% as the coefficient of variation. The RDAs were determined to be 2.5 mg/day and 15.0 mg/ day for the mid and late stages of pregnancy. Table 4 translates this calculation, and the values presented are the additional amounts required for the determination of the EAR and RDA of non-pregnant women.

Table 4. Additional amount during pregnancy: factors used to estimate the EAR and RDA

	Fetal iron storage (mg/stage)[1]	Placental iron storage (mg/stage)[1]	Required iron for blood increase (mg/stage)[2]	Total (mg/stage)	Total iron requirement throughout pregnancy (mg/day)[3]	Absorption Rate[4]	additional EAR (mg/day)[5]	additional RDA (mg/day)[6]
Early stage	25	5	0	30	0.32	0.15	2.1	2.6
Mid stage	75	25	150	250	0.25	0.25	10.7	12.9
Late stage	145	45	150	340	0.25	0.25	14.6	17.5

[1] According to the report by Bothwell, et al.(21)

[2] Calculated based on the reference BW (50.6kg), blood volume per BW (0.075L/kg), blood volume increase during pregnancy (30-50%), hemoglobin concentration standard during pregnancy (11g/dL), hemoglobin concentration in non-pregnant women (135g/L)(14), and iron content in hemoglobin (3.39mg/g)(8).

[3] Total (mg/stage)/ (280day)

[4] For early stage, the value for non-pregnant women was used. For mid and late stage, the values were based on the report by Barrett et al.(22)

[5] Total iron requirement (mg/day) / absorption rate

[6] Using 10% as the coefficient of variation

Among pregnant Japanese women, the prevalence of iron deficiency anemia (22.9%) was reported to be slightly higher than that among non-pregnant women (15.7%), in spite of their dietary iron intakes being similar(23). This indicates that there is a clear gap between dietary iron intake and iron deficiency anemia among pregnant women. This could be attributed to the fact that iron absorption significantly increases during pregnancy, as the demand increases. A balance study reported that dietary absorption rate was 39% among Japanese women in their 18th, 27th and 34th weeks of pregnancy(24). Using a dietary iron absorption rate of 40% during the mid and late stages, the EAR was estimated to be 6.7 mg/day for the mid stage, and 9.1 mg/day for the late stage. The RDA was estimated at 8.0 mg/day for the mid stage and 10.9 mg/day for the late stage. While these values may be more realistic, they were not established as the EAR and RDA for the DRIs, due to a lack of sufficient evidence.

2─1─6. Additional Amounts for Lactating Women (EAR, RDA)

The average iron requirement for lactation was calculated to be 2.2 mg/day, based on the iron concentration in the breast milk of Japanese mothers (0.426 mg/L)(25), average milk volume (0.78 L/day)(2,3), and absorption rate (15%): 0.426 × 0.78 ÷ 0.15. Rounding this value, the additional EAR for lactation was determined to be 2.0 mg/day. The additional RDA was determined as the EAR × 1.2, yielding a value of 2.5 mg/day by rounding 2.7 mg/day. These values were the additional EAR and RDA of non-pregnant women without menstruation. At the time of delivery, the actual loss of iron through blood (mean ± standard deviation) is 328±236 mL in primiparous women and 279±235 mL in multiparous women(26). This amount is clearly lower than the increase in the blood circulation during pregnancy, implying that the iron loss at delivery can be ignored for the establishment of the DRIs for lactating women. Indeed, the prevalence of iron deficiency anemia is lower among lactating women than non-pregnant or non-lactating women(23).

3. To Avoid Excessive Intake

The consumption of a regular diet does not lead to excessive iron intake; however, the inappropriate use of supplemental foods, iron-fortified foods, or medicinal iron for the treatment of anemia can lead to an overdose.

3─1. Method Used to Set the Tolerable Upper Intake level (UL)

3─1─1. Adult and Children (UL)

In a double-blind trial involving the administration of 60 mg/day of non-heme iron (fumarate iron), 18 mg/day of a mix of heme and non-heme iron (2 mg/day iron of pig blood-origin heme iron + 16 mg/day of non-heme iron) and a placebo, participants in the non-heme iron group more frequently reported symptoms such as constipation or other gastrointestinal effects(27). Inorganic iron supplement intake can also cause unidentified complaints, including gastric distress even in small doses of 2 mg/day or 10 mg/day as iron(28,29). In contrast, heme iron supplementation at 30 mg/day as iron, for 2 months, was not associated with gastric distress or changes in blood laboratory data(30).

For adults, chronic siderosis is a severe effect of long-term excess iron intake. A regular intake of beer containing a large amount of iron, or iron consumption due to the use of iron pans can cause Bantu siderosis. This has been estimated to occur at iron intakes greater than approximately 100 mg/day(31).

The FAO/WHO set the provisional maximal tolerable intake for iron at 0.8 mg/kg BW, excluding the use of iron oxide colorants, iron supplements for pregnancy and lactation, and medicinal iron(32). Taking this into consideration, the UL for adults aged 15 years or older was calculated using this value and the reference BWs for each age and sex category.

One study reported that a lower BW increase was observed among children aged 12-18 months after supplementation with 3 mg/kg/day of ferrous sulfate(33). According to the Food and Drug Administration (FDA), the most common causes of acute toxicity were accidental overdoses of medicinal iron or iron supplements, in children around 6 years of age; therefore, a limit of 60 mg/kg BW/day was set(34). This value was used to derive the UL for children aged 1-2 years; this was set as the lowest observed adverse effect level (LOAEL). Thus, the UL was calculated to be 2 mg/kg/day, using an uncertainty factor of 30. This uncertainty factor was obtained by multiplying 10 (to account for the extrapolation from the LOAEL to the UL) and 3 (for the protection of susceptible individuals). Among children aged 3-14 years, the UL was determined 1.6 mg/kg /day for those aged 3-5 years 1.4 mg/kg/day for those aged 6-7 years, 1.2 mg/kg/day for those aged 8-9 years, and 1.0 mg/kg/day for those aged 10-14 years.

3─1─2. Infants (UL)

A randomized controlled trial reported poorer growth, in terms of height and head circumference, in infants receiving iron supplementation (1 mg/kg iron) with a normal iron status (hemoglobin concentration >11 g/dL and serum ferritin concentration >50 μg/L)(35). Furthermore, in this study, the odds ratio (OR) for diarrhea was 2.4 in the iron supplementation group, compared to the placebo group, among infants with a hemoglobin concentration > 11 g/dL; the OR was 0.21 among infants with a hemoglobin concentration <11 g/dL. This iron supplementation is equivalent to approximately 7 mg/day for Japanese infants. In contrast, no adverse gastrointestinal effects were reported when 1-month-old infants were supplemented with 5 mg/day of non-heme iron for up to 1 year or 30 mg/day for up to 18 months(36), and when 3-month-old infants were supplemented with 10 mg/day of non-heme iron for up to 21 months(37). Similarly, no significant adverse gastrointestinal effects were reported when children aged 11-14 months were supplemented with 3 mg/kg BW/day (approximately 30 mg/day) of non-heme iron for 3 months(38). From these controversial findings for infants, it was difficult to set an LOAEL or NOAEL (no observed adverse effect level), and, consequently, no UL was established.

3─1─3. Pregnant and Lactating Women (UL)

Supplementation with 60 mg of fumarate iron suppressed zinc absorption in 5 lactating women(39). Similarly, stable zinc absorption was observed among 4 lactating women who received 120 mg/day of iron supplementation during pregnancy, and 76 mg/day of iron during lactation (zinc absorption usually rises during pregnancy)(40). However, a decreased serum zinc concentration was reported when 18 mg/day of iron supplements was administered to young pregnant women aged under 20 years; however, their iron status was improved(41). Although several reports have focused on zinc absorption in relation to iron supplementation, data were limited for the establishment of a UL for pregnant or lactating women.

Zinc

1. Background Information

1−1. Definition and Classification

Zinc is an element belonging to the zinc group (atomic number: 30, Zn). Approximately 2,000 mg of zinc is stored in the body(42), and this is predominantly distributed in the skeletal muscles, bones, skin, liver, brain and kidneys(43).

2. To Avoid Inadequacy

2−1. Method Used to Set the EAR and RDA

2−1−1. Adults (EAR, RDA)

No study has focused on zinc metabolism in the Japanese population. Therefore, the EARs for adults were calculated using the values from the US-Canada DRIs(44). The calculation methods used were as follows: 1) Estimate the nonintestinal losses of endogenous zinc (losses via urine, body surface and semen/menstrual blood), 2) Define the relationships between intestinal endogenous excretion (amount that moved from the tissues to feces via the intestine) and absorbed zinc, 3) Calculate the minimum quantity of absorbed zinc necessary to offset endogenous zinc losses, and 4) Calculate the dietary zinc intake corresponding to the average minimum quantity of absorbed zinc.

Considering the results pertaining to endogenous zinc excretion via the intestine, among 18-40-year-old men whose zinc intakes were lower than 20 mg/day, in the United Kingdom and US(45–51), the following equation was estimated:

Endogenous excretion via the intestine = 0.628 × quantity absorbed + 0.2784 mg/day

As total endogenous zinc excretion is the sum of endogenous excretion via the intestine and other routes, the total endogenous excretion can be calculated as follows:

Total endogenous excretion = 0.628 × quantity absorbed + 0.2784 + (urinary loss + integumental loss + loss through semen or menstrual blood)

According to a US balance study of 11 men (mean BW: 75.5 kg), the urinary loss, integumental loss, and loss through semen were 512, 525 and 111 μg/day, respectively(52). Using the 0.75th power of the BW ratio and the reference BW for those aged 18-29 years, the total endogenous excretion was extrapolated as follows:

Men: Total endogenous excretion = 0.628 × quantity absorbed + 0.2784 + (0.448 + 0.460 + 0.097) (mg/day)

Women: Total endogenous excretion = 0.628 × quantity absorbed + 0.2784 + (0.376 + 0.386 + 0.082) (mg/day)

Therefore, the minimal intake necessary to maintain zinc balance among adults aged 18-29 years, with a reference BW, was calculated to be 3,450 mg/day for men and 3,015 mg/day for women.

However, the relationship between zinc absorption and zinc intake is expressed by the following equation(45–51): quantity of absorbed zinc = 1.113 × zinc intake$^{0.5462}$. Therefore, the quantities of absorbed zinc were calculated to be 7,936 mg/day and 6,199 mg/day, respectively. Using these values as reference for the EAR, the EAR for each age group was determined through extrapolation, using the 0.75th power of the BW ratio.

The RDA was determined as the EAR × 1.2, using 10% as the coefficient of variation. For women aged 18-29 years, the RDA was determined by smoothing the value calculated.

2─1─2. Children (EAR, RDA)

The EAR for adolescents aged 12-17 years was determined by the extrapolation of the EAR for adults, using the 0.75th power of the BW ratio and the growth factors. The RDA was determined as the EAR × 1.2, using 10% as the coefficient of variation.

In a study of Japanese children (mean BW: 16.34 kg), the minimal intake necessary to maintain zinc balance was estimated to be 3.87 mg/day(53). Using data on the growth factors and integumental zinc loss among US men with a BW of 75.5 kg (0.51 mg/day)(52), the integumental zinc loss of children with a BW of 16.34 kg was estimated to be 0.16 mg/day. The EAR for children with a BW of 16.34 kg was determined by the extrapolation of 4.03 (the sum of the minimal intake required to maintain zinc balance and integumental loss). The EAR for children aged 1-11 years was determined by the extrapolation of 4.03 mg/day to each age group, using the 0.75th power of the BW ratio and growth factors. The RDA was determined as the EAR × 1.2, using 10% as the coefficient of variation.

2─1─3. The Additional Amount for Pregnant and Lactating Women

The decreases in the plasma zinc concentration are reported to be 72.7 μg/dL, 63.8 μg/dL and 62.1 μg/dL, and 63.3 μg/dL in the early term, mid term and late term of pregnancy, and at delivery, respectively(54), and these are the additional intakes required for pregnant women. The EAR for pregnant women (amount to be added to the value of non-pregnant women) was determined to be 1 mg/day by dividing the zinc storage during pregnancy (0.40 mg/day)(55) by the zinc absorption of non-pregnant women (27%), and rounding. The RDA (amount to be added to the value of non-pregnant women) was determined as the EAR × 1.2, using 10% as the coefficient of variation.

The concentration of zinc in breast milk was calculated to be 1.13 mg/day, using the reported average concentration in Japanese women (1.45 mg/L)(56), and the average milk volume (0.78 L/day)(2,3). The EAR (amount to be added to the value of non-pregnant women) was calculated to be 2.13 mg/day, using the above value and an absorption rate of 53%(57). The RDA (amount to be added to the value of non-pregnant women) was calculated as the EAR × 1.2, using 10% as the coefficient of variation. These values were rounded to yield a value of 3 mg/day.

2─2. Method Used to Set AI

2─2─1. Infants (AI)

Like in the case of the previous DRIs, the AI for Japanese infants aged 0-5 months was set at 2.0 mg/day in accordance with the US-Canada DRIs(44). Several studies have focused on the breast milk of Japanese mothers(56,58–60). Using the reported data on the zinc concentration in the breast milk of Japanese mothers (1.45 mg/L)(56), and average breast milk intake (0.78 L/day)(2,3), the average zinc intake was estimated to be 1.13 mg/day among infants aged 0-5 months. However, there have been no reports on zinc intake and deficiency among Japanese infants since the previous DRIs; therefore, the AI was not changed.

The AI for infants aged 6-11 months was determined as the mean of the following values: 1) the sum of the zinc intake from complementary food and infant formula (3.1 mg/day) (61); and 2) the extrapolation of 2 mg/day using the 0.75th power of the BW ratio (2.6 mg/day). Thus, the AI was determined as 3 mg/day by rounding the calculated mean (2.85 mg/day).

3. To Avoid Excessive Intake

Excessive zinc intake can occur when supplemental foods are used inappropriately. There is no evidence on the adverse effects associated with the intake of naturally occurring zinc in food.

Based on the results of a study in which 18 women in the US (age 25-40 years) were administered 50 mg/day of zinc supplements(62,63), the LOAEL of zinc was estimated to be 60 mg/day in women with a BW of 61 kg. Using this value and an uncertainty factor of 1.5(44), the UL for adults was determined to be 0.66 mg/kg/day × the reference BW of each age and sex group. No UL was determined for children, infants, pregnant women and lactating women as no relevant data were available.

Copper

1. Background Information

1─1. Definition and Classification

Copper (atomic number: 29, Cu) is a transition metal element. Approximately 80 mg of copper exists in the human body, 50% of which is distributed in the muscles and bones. As excess intracellular copper is associated with toxicity(64), the homeostasis of copper needs to be regulated by absorption and excretion(65). The liver is a key site in the maintenance of plasma copper concentrations(66,67).

2. To Avoid Inadequacy

2─1. Method Used to Set the EAR and RDA

No studies have focused on the dietary copper requirement in Japan. Therefore, the EAR for copper was determined using the plasma copper concentration, serum ceruloplasmin concentration, and erythrocyte superoxide dismutase activity (SOD), in accordance with the US-Canada DRIs(68). Although the use of these indicators for the DRIs has some limitations(69), no better indicator has been suggested till date(69–74).

2─1─1. Adults (EAR, RDA)

Two studies examining the effects of copper intake on the copper status of men in the US reported that the amounts of copper intake that showed no difference in the copper status indicators mentioned above were 0.66 mg/day and 0.79 mg/day(75,76). While a study suggested that an intake of 0.66 mg/day was not sufficient for the maintenance of whole-body copper metabolism(77), in another study, no change in the biomarkers was observed when the dietary copper intake was increased from 0.8 mg/day to 7.5 mg/day(78). Several reviews have suggested that the appropriate intake of copper is between 0.8 and 0.94 mg/day(69–71). From these values, the minimal copper intake required was estimated to be 0.79 mg/day. The EAR for each sex and age group was determined by extrapolation, using the reference BW of the US-Canada DRIs (men aged 18-30 years, 76.0 kg) and the 0.75th power of the BW ratio. The RDA was determined as the EAR × 1.3, using 15% as the coefficient of variation.

One report recommended a copper intake of 0.6 mg/1,000 kcal for the prevention of the decrease in the blood copper concentrations among elderly patients with enteral nutrition therapy, who tend to have copper deficiency(79). However, no report has stated that the requirement for healthy elderly individuals is higher than that of adults aged 18-69 years. Therefore, the EAR for those aged over 70 years was determined to be the same as that for younger adults.

2─1─2. Children (EAR, RDA)

The EAR was extrapolated from the values for adults, using the 0.75th power of the

BW ratio and growth factors. The RDA was determined as the EAR × 1.3, using 15% as the coefficient of variation.

2─1─3. The Additional Amount for Pregnant and Lactating Women

A full-term fetus has approximately 13.7 mg of copper(80). A study using a stable isotope reported that the dietary copper absorption is 44-67% among healthy individuals(77). Therefore, using a dietary absorption rate of 60%, the additional EAR for pregnant women was determined as 1.0 mg/day (13.7 mg ÷ 280 days ÷ 0.6 = 0.8 mg/day, rounded). The additional RDA was determined as the EAR × 1.3, using 15% as the coefficient of variation.

For lactating women, based on the average copper concentration in the breast milk of Japanese mothers (0.35 mg/L)(56), the average milk intake (0.78 L/day)(2,3), and a copper absorption rate of 60%, the additional EAR was determined to be 0.5 mg/day (0.35 × 0.78 ÷ 0.6 = 0.455 mg/day, rounded). The additional RDA was determined as the EAR × 1.3, using 15% as the coefficient of variation.

2─2. Method Used to Set Adequate Intake

2─2─1. Infants (AI)

The average copper concentrations in the breast milk of Japanese women were estimated to be 0.35 mg/L (age 0-5 months) and 0.16 mg/L (age 6-11 months)(56). For infants aged 0-5 months, the AI was determined as 0.3 mg/day, using the average milk volume (0.78 L/day)(2,3) (0.35 mg/L × 0.78 L/day). For infants aged 6-11 months, based on the intake from breast milk (0.16 mg/L(56) × 0.53 L/day(81,82) and the intake from complementary food (median of 0.05-0.34 mg/day)(54), the AI was estimated to be 0.28 mg/day by rounding 0.3 mg/day.

3. To Avoid Excessive Intake

Excessive copper intake can occur when supplemental foods are used inappropriately. No studies have reported on the presence of adverse effects due to the intake of naturally occurring copper in food.

Based on the fact that a study with an administration of 10 mg/day of copper supplements did not observe adverse effects(83), the NOAEL was estimated to be 10 mg and the UL was set at 10 mg/day, using an uncertainty factor of 1.0. No UL was determined for children, infants, pregnant women, and lactating women, as no relevant data were available.

Manganese

1. Background Information

1─1. Definition and Classification

Manganese (atomic number: 25, Mn) is a group 7 element, 12-20 mg of which is present in the adult human body, uniformly distributed across the tissues and organs(84).

2. To Avoid Inadequacy

2─1. Method Used to Set the AI

Balance studies, pertaining to manganese, have been conducted in Japan and other countries(85,86). However, only a small percentage of dietary manganese is absorbed, and most of it is excreted in feces(84). Therefore, short-term balance data could not be used to estimate the average requirement for manganese, in accordance with the US-Canada DRIs(87). The AI was set using the Japanese dietary manganese intake, which most likely far exceeds the requirement for manganese balance.

2─1─1. Adults (AI)

Based on a review of the manganese intake of Japanese individuals, the average manganese intake of adults was 3.8 ± 0.8 mg/day in men, 3.8 ± 1.4 mg/day in women, and 3.6 ± 1.1 mg/day in adults, as examined using duplicate methods(88). Another study that examined weighed dietary records reported that the median manganese intake was 4.5 mg/day in men, and 3.9 mg/day in women (aged 30-69 years)(89). To account for the differences in the energy intake between men and women, the AI for adults aged 18 years and older was set at 4.0 mg/day in men, and 3.5 mg/day in women.

2─1─2. Children (AI)

Although several studies have focused on manganese intake among Japanese children(90,91), the estimated intake has a wide range. Therefore, the AI for children and adolescents was determined by the extrapolation of the value for adults, using the 0.75th power of the BW ratio and growth factors.

2─1─3. Infants (AI)

Since there are differences in the concentration of manganese in the breast milk of lactating mothers in Japan and the US(56,92–94), the current DRIs used Japanese data. For infants aged 0-5 months, using the average manganese concentration in the breast milk of Japanese women (11 μg/L)(56), and the average milk intake (0.78 L/day)(2,3), the AI was set at 0.01 mg/day by rounding 8.6 μg/day. For infants aged 6-11 months, the average manganese intake was estimated as 0.44 mg/day(61). Therefore, taking the manganese intake from breast milk to be 5.8 μg/day (manganese concentration in breast milk :11 μg/L(56), and average milk intake to be 0.53

L/day [81,82]), the AI was set at 0.5 mg/day by rounding 0.446 mg/day.

2─1─4. Pregnant and Lactating Women (AI)

The AI for pregnant women was the same as that for non-pregnant women, due to a lack of data on the manganese intake required during pregnancy.

For lactating women, milk production can lead to a loss of 172-286 μg/day of dietary manganese [manganese concentration in breast milk: 11 μg/L × average milk volume: 0.78 L/day ÷ absorption rate: (0.03-0.05) = 172-286 μg/day]. However, this value is much lower than the AI of non-pregnant women; therefore, the AI was set at a value that was equal to that of non-pregnant women.

3. To Avoid Excessive Intake

Excessive manganese intake can occur in the case of strictly vegan diets, and the inappropriate intake of supplemental foods.

The manganese intake from meals comprising grains, beans, and nuts is estimated to be no higher than 10.9 mg/day(95). Similarly, vegetarians may have an intake of 13-20 mg/day of manganese(96). The US-Canada DRIs estimated the NOAEL of manganese to be 11 mg(88).

From these reports, the UL for adults was set at 11 mg/day, using a NOAEL of 11 mg/day and an uncertainty factor of 1.0. No UL was determined for children, infants, pregnant women, and lactating women, as no relevant data were available.

Iodine

1. Background Information

1─1. Definition and Classification

Iodine (atomic number: 53, I) is a halogen element. A total of 70-80% of the iodine in the body is distributed in the thyroid, as it is an essential component of the thyroid hormone.

2. To Avoid Inadequacy

2─1. Method Used to Set the EAR and RDA

Japanese people routinely consume marine products, which contain high levels of iodine, and their average iodine intake is estimated to be much higher than in other populations. However, since there are no Japanese studies available for the setting of the requirement of iodine intake, the EAR and RDA were determined based on studies conducted in Western countries.

2─1─1. Adults (EAR, RDA)

The EAR was determined through the measurement of thyroid iodine accumulation and turnover. Based on the results of 2 US studies, the accumulation of radioiodine by the thyroid gland was estimated to be 95 μg/day(97,98) in adults. This value was used for the EAR of men and women. In accordance with the US-Canada DRIs(99), the RDA was determined to be 130 μg/day, using the EAR × 1.4, and a coefficient of variation of 20%.

2─1─2. Children (EAR, RDA)

For children and adolescents aged 1-17 years, the EAR was determined by the extrapolation of the EAR for adults aged 18-29 years using the 0.75th power of the BW ratio and growth factors. The RDA was determined as the EAR × 1.4, using 20% as the coefficient of variation.

2─1─3. The Additional Amount for Pregnant and Lactating Women

According to a Western study, the iodine turnover in newborn infants ranged from 50-100 μg/day(100). Using the median value (75 μg/day), the EAR was determined as the amount to be added to the value of non-pregnant women.

A balance study examining 5 pregnant women reported that the iodine intake necessary for the maintenance of iodine balance was approximately 160 μg/day(101), which is similar to the sum of the EAR for non-pregnant women and the additional EAR for pregnant women (170 μg/day). The RDA (to be added to the RDA for non-pregnant women) was determined as the EAR × 1.4, using 20% as the coefficient of variation.

The iodine loss from breast milk may be large in Japanese women. However, this could be caused by a high intake of iodine; this suggests that there is no requirement for an increase in the intake, based on the high iodine concentration of breast milk. Therefore, for lactating women, the EAR was determined to be the same as the AI for infants aged 1-5 months. Estimating the iodine absorption to be 100%, the additional EAR was set at 100 μg/day. The additional RDA was determined as the EAR × 1.4, using 20% as the coefficient of variation. The WHO set the recommendation for iodine intake at 250 μg/day for pregnant or lactating women(102).

2─2. Method Used to Set the AI

2─2─1. Infants (AI)

The iodine content of the breast milk of Japanese mothers is reported to be 77-3,971 μg/L (n＝39, median 172 μg/L)(103), or 83-6,960 μg/L (n＝33, median 207 μg/L)(104). When using the median of these values (189 μg/L), and the average milk intake(2,3), the iodine intake of infants aged 0-5 months can be estimated as 147 μg/day; this is much higher than the AI in the US-Canada DRIs (110 μg/day)(99). Therefore, the AI for infants aged 0-5 months was determined to be 100 g/day, considering the value of the US-Canada DRIs, and the difference in the body size between Japanese individuals and those from the US. The WHO set the recommendation for iodine intake at 90 μg/day for infants(105).

For infants aged 6-11 months, the iodine intake from complementary food ranges widely(106,107), and it is difficult to use these values for the estimation of AI. Therefore, the AI for infants aged 6-11 months was determined by extrapolating the AI for infants aged 0-5 months using the 0.75th power of the BW ratio.

3. To Avoid Excessive Intake

3─1. Dietary Intake

The high iodine intake among Japanese individuals has been examined from several angles. Based on a chemical iodine analysis of duplicate diets(108), and the measurement of urinary iodine excretion(109,110), the iodine intakes were regularly lower than 500 μg/day with an intermittent intake of 2-10 mg/day. Based on the annual reports on the consumption of seaweeds, the average iodine intake was estimated as 1.2 mg/day(111). A review of the iodine intake among Japanese individuals showed that the average intake was 1-3 mg/day(112). From these results, the iodine intake in Japanese populations can be estimated as 1-3 mg/day for diets without seaweed (less than 500 μg/day) and those with seaweed. Recent reports on the iodine intake in Japan support this value(113,114).

3─2. Method Used to Set the UL

3─2─1. Adults (UL)

Initially, excessive iodine intake induces hypothyroidism and goiter, a phenomenon referred to as the Wolff-Chaikoff effect. However, this effect does not occur due to a continuous excessive intake of iodine; it is a result of a phenomenon referred to as the “escape phenomenon,” which maintains the thyroid hormone synthesis within the normal range(115). Excessive iodine intake is assumed to affect Japanese individuals to a lower extent, due to their unique iodine intake pattern and the escape phenomenon. However, despite the presence of the escape phenomenon, excessive iodine intake decreases the synthesis of the thyroid hormone, which can induce hypothyroidism, or goiter at worst(99).

In the US-Canada DRIs, using an iodine intake value of 1.7 mg/day, which results in hypothyroidism, as the LOAEL, the UL was set at 1.1 mg/day among adults(99). Some reports pointed to a higher risk of goiter among those whose iodine intake exceeded 1.5 mg/day (mainly from water) in China and Africa(116,117). In contrast, although the iodine intake in Japanese individuals can be estimated at an average of 1-3 mg/day, the prevalence of hypothyroidism or goiter is exceedingly low. Therefore, for Japanese adults, 3 mg/day was regarded as an upper limit--the NOAEL. Using this value, and an uncertainty factor of 1, the UL was estimated as 3.0 mg/day.

According to several Japanese case studies, unusual iodine intakes, such as intakes of 28 mg/day for a 1-year period (mainly from seaweed soup)(118), or consuming one pack of seaweed chips a day(119), led to the development of hypothyroidism or goiter. Some Japanese experimental studies reported that an iodine intake (seaweed) of 35-70 mg/day for 7-10 days increased the serum thyroid-stimulating hormones (TSH) levels(120), and an iodine preparation of 27 mg/day for 28 days decreased the thyroid activity and increased the thyroid volume(121). Taking these values as the NOAELs, the ULs were estimated as 2.8, 3.5 and 2.7 mg/day, respectively, using an uncertainty factor of 10. An epidemiological study examining people living in the coastal areas of Hokkaido reported that an increased prevalence of hypothyroidism was observed among those with an iodine intake greater than 10 mg/day, based on a urine analysis(122,123). As the urinary iodine concentration was measured only once, this value could not be used for the determination of the UL.

Based on these reports, the UL was estimated to be around 3.0 mg/day; therefore, the UL for adults was set at this value. One study reported that the average iodine intake among those who did not consume seaweed was only 73 μg/day(124). Therefore, as the UL applies to habitual iodine intake, it is not necessary to restrict the habitual intake of seaweed.

3─2─2. Children (UL)

A study examining children aged 6-12 years, worldwide, reported that an iodine intake greater than 500 μg/day could be harmful, as the thyroid volume of Japanese children living in the coastal areas of Hokkaido was significantly larger than that of other populations, and their estimated average iodine intake was 741 μg/day(125). Therefore, the UL was set at 500 μg/day for children aged 6-17 years.

The UL for children aged 1-5 years was extrapolated from that of those aged 6-7 years, using the 0.75th power of the BW ratio, and the average of the values for boys and girls was adopted as the UL. Among children aged 12-17 years, the UL was set at 1.2 g/day for the 12-

14 years age group, and 2 mg/day for the 15-17 years group, considering the values for those aged 10-11 years and adults. As the UL applies to habitual iodine intake, it is not necessary to restrict the habitual intake of seaweed.

3─2─3. Infants (UL)

A decrease in serum thyroid hormone levels, and an increase in TSH levels were observed in low-birth weight Korean infants whose iodine intake from breast milk exceeded 100 μg/kg/day(126). Using this value, and an uncertainty factor of 3, 33 μg/kg/day was set as the value for the determination of the UL for each age category. Using this value and the reference BW, the ULs were calculated as 208 μg/day (in boys aged 1-5 months), 195 μg/day (in girls aged 1-5 months), 290 μg/day (in boys aged 6-11 months), and 267 μg/day (in girls aged 6-11 months). However, as the participants of the Korean study were low-birth weight infants, the UL was determined as 250 μg/day by rounding the average value of the four values calculated above. Although this UL applies to habitual iodine intake, breast-feeding mothers need to pay attention to the UL of iodine intake, as infants display a higher sensitivity to iodine(127).

3─2─4. Pregnant and Lactating Women (UL)

In Japanese case reports focusing on hypothyroidism in infants, the mothers' iodine intakes were reported to be 1.9-4.3 mg/day(128)(129). However, it is difficult to use these values for the setting of the UL, due to the inaccuracy of the dietary iodine assessment. The iodine intake of over 500 healthy pregnant or lactating Japanese women was estimated to be 1.4-1.7 mg/day, using a food frequency questionnaire focusing on iodine intake(130), indicating that the iodine intake of pregnant women is not very different from that of normal adults. As infants may display a higher sensitivity to iodine(127), pregnant women should pay attention to excess iodine intake. Therefore, using the UL for adults and an uncertainty factor of 1.5, 2 mg/day was set as the UL for pregnant women. For lactating women, a special UL was not set due to a lack of relevant data. However, a consistent excessive intake of iodine is not recommended for lactating women compared to non-lactating women.

Selenium

1. Background Information

1─1. Definition and Classification

Selenium (atomic number: 34, Se) is a group 16 element. Fish and shellfish are known to contain high levels of selenium. The amount of selenium in plant foods and stock farm products depends on the type of soil and feed, respectively(131).

2. To Avoid Inadequacy

2─1. Method Used to Set the EAR and RDA

The EAR and RDA were determined for the prevention of selenium deficiency disorders such as Keshan disease.

2─1─1. Adults (EAR, RDA)

Although the synthesis of selenium-containing protein is strongly associated with selenium intake, stability is maintained at a certain intake level(132). The association between plasma glutathione peroxidase (GPX) and selenium intake has been well-examined. In a study that examined a low-selenium area of China, a saturation in the plasma GPX activity was observed at a selenium intake of 41 μg/day in men with an average weight of 60 kg(133). Together with this result, the US-Canada DRIs used the findings of another study that showed that an intake level of 38 μg/day resulted in saturation(134); accordingly, the EAR was set at 45 μg/day using these average values, at a BW of 76 kg(135). However, the WHO concluded that selenium deficiency may be prevented when two-third of the value of saturated plasma GPX activity is maintained(136).

Several studies have reported the absence of deficiency at low selenium intakes, with unsaturated serum or erythro GPX activity(137)(138)(139), indicating that maintaining two-third of the value of saturated plasma GPX activity is sufficient. Based on the aforementioned Chinese study(133), the selenium intake necessary to maintain two-third of the value of saturated plasma GPX activity was estimated to be 24.2 μg for adults with a BW of 60 kg, using the WHO equation(136). The EAR for selenium in adults aged 18 years and older was calculated by the extrapolation of this value, using the 0.75th power of the BW ratio. The RDA was determined as the EAR × 1.2, using 10% as the coefficient of variation.

2─1─2. Children (EAR, RDA)

The EAR for children aged 1-17 years was determined by the extrapolation of the value for adults (24.2 μg/day, BW 60 kg), using the 0.75th power of the BW ratio and growth factors. The RDA was determined as the EAR ×1.2, using 10% as the coefficient of variation.

2─1─3. The Additional Amount for Pregnant and Lactating Women

Based on the average body selenium concentration in fetuses (250 μg/kg)(96), and the sum of the placental and birth weights (3.5 kg), the fetal and placental selenium storage was estimated to be about 900 μg during pregnancy. The average blood selenium concentration has been reported to be 170-198 μg/L (average 184 μg/L)(140). Therefore, the increased selenium requirement due to an increase in the blood volume (1.5 L) during pregnancy can be estimated as about 300 μg. Using a dietary selenium absorption rate of 90%(132), the EAR added to the value of non-pregnant women, was set at 5 μg/day ((900 + 300) μg/0.9/280 days, rounded). The additional RDA was determined as the EAR × 1.2, using 10% as the coefficient of variation.

For lactating women, the additional EAR was determined to be 15 μg/day, based on the average selenium concentration in the breast milk of Japanese women (17 μg/L)(56), average milk volume (0.78 L/day)(2,3), and a dietary selenium absorption rate of 90%(132). The additional RDA was determined as the EAR × 1.2, using 10% as the coefficient of variation.

2─2. Method Used to Set the AI

2─2─1. Infants (AI)

Based on the average selenium concentration in the breast milk of Japanese women (17 μg/L)(56), the AI for infants aged 0-5 months was determined as 15 μg/day, using the average milk intake (0.78 L/day).

A study reported that there was no difference in the plasma selenium concentration between exclusively-breastfed infants and infants fed formula and complementary food (aged 12 months)(141). Therefore, the AI for infants aged 6-11 months was calculated by the extrapolation of the AI for infants aged 0-5 months (13.3 μg/day), using the 0.75th power of the BW ratio, and was set at 15 μg/day for both boys and girls.

3. To Avoid Excessive Intake

Excess selenium intake can result from inappropriate supplemental food intake.

3─1. Method Used to Set the UL

3─1─1. Adults and Children (UL)

Based on a Chinese report on chronic selenium intoxication, the minimum intake among 5 patients was estimated as 913 μg/day (average BW 60 kg). After recovery, the average selenium intake was estimated as 800 μg/day. From these results, the LOAEL was set at 913 μg/day (15.2 μg/kg weight/day), and the NOAEL at 800 μg/day (13.3 μg/kg weight/day)(142). In a study on selenium intoxication among farm animals in the US, no health effect was found among 142 farmers with a maximum selenium intake of 724 μg/day(143). This supports the setting of an LOAEL of 800 μg/day. This value was used as the LOAEL, and the UL was determined using an uncertainty factor of 2, as well as the reference BW for each age and sex category.

3―1―2. Infants (UL)

The US-Canada DRIs set the UL at 47 μg/L using a breast milk selenium concentration of 60 μg/L, as almost no selenium intoxication was observed at this level(135,144,145). However, a report stated that there were very few cases of selenium intoxication in the hair and nails(145). Therefore, the current DRIs did not set the UL due to insufficient evidence.

3―1―3. Pregnant and Lactating Women (UL)

The UL for pregnant or lactating women was not determined due to a lack of adequate information.

Chromium

1. Background Information

1─1. Definition and Classification

Chromium (atomic number: 24, Cr) is group 6 element, and is predominantly consumed as trivalent chromium in the regular diet.

2. To Avoid Inadequacy

2─1. Method Used to Set the AI

2─1─1. Adults and Children (AI)

The WHO(146) and a UK study(147) estimated the requirement of chromium to be 24.5 μg/day, based on a balance study(148). However, that study examined only a small number of elderly people, and did not estimate the intake required for the maintenance of equilibrium; therefore, it was not regarded as evidence for the setting of the EAR. As it was difficult to determine the EAR, the AI was determined based on the chromium intake, in accordance with the US-Canada DRIs(149).

According to a report measuring the chromium content of diets, the chromium intake was estimated as ranging from 20-80 μg/day among adults, including those in Japan(150). In contrast, the chromium intake among Japanese individuals was estimated to be about 10 μg/day, on using the Japanese Standard Food Composition Table 2010(151)(152). These results indicate that there may be differences between the findings of chemical analyses and intake estimations. Therefore, although it is difficult to accurately estimate the chromium intake of Japanese people, it may be more appropriate to use the estimated intake using dietary assessment (10 μg/day) (151)(152). Thus, the AI was set at 10 μg/day. For children, the AI was not determined as there was no information on selenium intake.

2─1─2. Infants (AI)

According to a Japanese report on the chromium concentration of breast milk, the chromium intake was less than 1 μg/L among 48% of participants and 1-2 μg/L among 25%; only 8% of the participants had an intake higher than 5 μg/L (median: 1.00 μg/L)(153). These results were higher than the chromium concentration of breast milk used in the US-Canada DRIs (0.25 μg/L) (154). However, the Japanese intake is within the intake range of the investigation by the WHO/IAEA(155). Based on the median chromium concentration in the breast milk of Japanese mothers (1.00 μg/L), and average milk volume (0.78 L/day)(2,3), the AI for infants aged 0-5 months was determined at 0.8 μg/day. For infants aged 6-11 months, this value was extrapolated to calculate the AI, using the 0.75th power of the BW ratio.

2─1─3. Pregnant and Lactating Women (AI)

For pregnant or lactating women, the AI was determined to be the same as that for non-pregnant/non-lactating adults.

3. To Avoid Excessive Intake

Although excess hexahydric chromium can accumulate in the kidneys, spleen, liver, lung and bones, and cause toxicity(156), hexahydric chromium is artificially produced and it occurs naturally in low amounts. The present DRIs did not consider hexahydric chromium in the determination of the UL.

Some reports focused on the health effects associated with chromium supplementation(157,158). However, those reports did not examine the influence of other medications or supplements. The UL for chromium was not set due to a lack of sufficient data on the quantitative association between trivalent chromium intake and possible adverse effects.

4. For the Prevention of the Development and Progression of Lifestyle-related Diseases

A meta-analysis(159) found that while chromium supplementation had a positive effect on blood glucose and HbA1c levels among patients with type 2 diabetes, there was no effect in those without diabetes, including those with impaired glucose tolerance. The studies included in the meta-analysis used chromium chloride and picolinate chromium intake levels (200-1,000 μg/day), and chromium yeast levels (10-400 μg/day).

The findings of other relevant studies on diabetes patients are inconsistent(160,161). However, one study reported the absence of an effect of chromium supplementation (500 or 1,000 μg/day) in those with impaired glucose tolerance, elevated fasting blood glucose levels, or metabolic syndrome(162). Furthermore, decreased insulin sensitivity was observed in normal-weight participants without diabetes who were administered 1,000 μg/day of chromium supplementation(163).

Molybdenum

1. Background Information

1─1. Definition and Classification

Molybdenum (atomic number: 42, Mo) is among the chromium group elements.

2. To Avoid Inadequacy

2─1. Method Used to Set the EAR and RDA

2─1─1. Adults (EAR, RDA)

The EAR for molybdenum was determined based on the results of a balance test of 4 men in the US(164). In this study, a positive balance of molybdenum was observed without any molybdenum deficiency in all participants consuming 22 μg/day of molybdenum for 102 days. Estimating the integumental and sweat molybdenum loss to be 3 μg/day, 25 μg/day was set as a reference value for the calculation of the EAR. Using the average BW of the study (76.4 kg) and the 0.75th power of the BW ratio, the EAR was determined by the extrapolation for each age and sex group.

The RDA was determined as the EAR × 1.2, using 10% as the coefficient of variation. It is important to note that this EAR and RDA are dependent on the result of one study, and the reliability might need to be considered cautiously; nevertheless, the US-Canada DRIs and WHO have adopted the same method(154,165).

2─1─2. Children (EAR, RDA)

There is little evidence on the EAR of children, and it is difficult to extrapolate the EAR for adults to that of children, since the EAR for adults was determined based on a study of 4 individuals. The EAR and RDA were not determined for children aged under 18 years.

2─1─3. The Additional Amount for Pregnant and Lactating Women

The additional EAR for pregnant women was not determined due to a lack of data.

For lactating women, based on the average molybdenum concentration of the breast milk of Japanese mothers (3.0 μg/L)(153,166), the average milk volume (0.78 L/day) (2,3), and the Japanese dietary molybdenum absorption rate (93%)(167), the EAR was determined as 3 μg/day (3.0 × 0.78 ÷ 0.93, rounded), as the amount to be added to that for non-pregnant women. The RDA was determined as the EAR ×1.2, using 10% as the coefficient of variation.

2─2. Method Used to Set AI

2─2─1. Infants (AI)

Two reports focused on the molybdenum concentration of breast milk in Japanese women. One study reported that the level was 0.8-34.7 μg/L (median 2.9 μg/L)(166), while another reported the range to be 0.1 to 25.91 μg/L (median 3.18 μg/L)(153). Based on the average of these median values (3.0 μg/L), and the average milk volume (0.78 L/day)(2,3), the EAR for infants aged 0-5 months was determined as 2 μg/day.

For infants aged 6-11 months, the molybdenum intake from complementary foods should be considered. One study estimated the molybdenum intake to be 6.5 μg/day in children aged 6-8 months, and 12.5 μg/day in children aged 9-11 months, based on the content analysis of commercially available complementary foods in Japan(168). Using the average of these values, the AI for infants aged 6-11 months was determined at 10 μg/day.

3. To Avoid Excessive Intake

3─1. Example of Molybdenum Intoxication

Few studies have focused on molybdenum intoxication. One study reported on the relationship between molybdenum intake and high uric acid levels, and the development of gout symptoms(169). Using the results of that study, the American Environment Preservation Association set an LOAEL of 140 μg/kg weight, and a reference value of 5 μg/kg for chronic oral molybdenum intake, using an uncertainty factor of 30(170). The WHO uses the same reference value(165). However, the National Research Conference of America has concluded that the influence of molybdenum on high uric acid levels and the development of gout has not been substantially established in the aforementioned study(171).

3─2. Dietary Intake

Since molybdenum is present in high quantities in grains and beans, consuming a strict vegetarian diet may lead to a high intake of molybdenum. The molybdenum intake in Japanese populations has been reported to be 225 μg/day, on average(172). Another study reported that the molybdenum intake was higher than 300 μg/day when a soybean-rich diet was consumed(167). In contrast, 540 μg/day was reported as the mean molybdenum intake in Japanese women (mean BW: 49.1 kg) consuming a strict vegetarian diet; however, no negative effect was observed in that study(173).

3─3. Method Used to Set the UL

A study reported that no negative effect was observed among 4 Americans who received oral administration of molybdenum stable isotope after the consumption of 1,490 μg/day of molybednum for 24 days(174). The UL was determined using this result, and was set as the NOAEL. The NOAEL was calculated as 1,500 μg/day (total molybdenum intake)/82 kg (the mean BW) = 18 μg/kg weight/day. Using an uncertainty factor of 2, 9 μg/kg/day was set as the reference value for the calculation of the UL. The ULs were calculated as 550 μg/day for men, and 450 μg/men for women, using the reference BW for those aged over 70 years (the lowest among all adults) after rounding. These values are consistent with the results of the aforementioned Japanese study that reported no negative effects among vegetarian women consuming approximately 500 μg/day of molybdenum(173).

The UL was not determined for infants, children, pregnant women, and lactating women due to a lack of data.

DRIs for Iron (mg/day) [1]

Gender	Males				Females					
Age etc.	EAR	RDA	AI	UL	Not menstruating		Menstruating		AI	UL
					EAR	RDA	EAR	RDA		
0-5 months	—	—	0.5	—	—	—	—	—	0.5	—
6-11 months	3.5	5.0	—	—	3.5	4.5	—	—	—	—
1-2 years	3.0	4.5	—	25	3.0	4.5	—	—	—	20
3-5 years	4.0	5.5	—	25	3.5	5.0	—	—	—	25
6-7 years	4.5	6.5	—	30	4.5	6.5	—	—	—	30
8-9 years	6.0	8.0	—	35	6.0	8.5	—	—	—	35
10-11 years	7.0	10.0	—	35	7.0	10.0	10.0	14.0	—	35
12-14 years	8.5	11.5	—	50	7.0	10.0	10.0	14.0	—	50
15-17 years	8.0	9.5	—	50	5.5	7.0	8.5	10.5	—	40
18-29 years	6.0	7.0	—	50	5.0	6.0	8.5	10.5	—	40
30-49 years	6.5	7.5	—	55	5.5	6.5	9.0	10.5	—	40
50-69 years	6.0	7.5	—	50	5.5	6.5	9.0	10.5	—	40
70+ years	6.0	7.0	—	50	5.0	6.0	—	—	—	40
Pregnant women (additional)										
Early stage					+2.0	+2.5	—	—	—	—
Mid to late stage					+12.5	+15.0	—	—	—	—
Lactating women (additional)					+2.0	+2.5	—	—	—	—

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[1] Developed excluding persons with menorrhagia (menstrual blood loss of 80mL/period or more).

DRIs for Zinc (mg/day)

Gender	Males				Females			
Age etc.	EAR	RDA	AI	UL	EAR	RDA	AI	UL
0-5 months	—	—	2	—	—	—	2	—
6-11 months	—	—	3	—	—	—	3	—
1-2 years	3	3	—	—	3	3	—	—
3-5 years	3	4	—	—	3	4	—	—
6-7 years	4	5	—	—	4	5	—	—
8-9 years	5	6	—	—	5	5	—	—
10-11 years	6	7	—	—	6	7	—	—
12-14 years	8	9	—	—	7	8	—	—
15-17 years	9	10	—	—	6	8	—	—
18-29 years	8	10	—	40	6	8	—	35
30-49 years	8	10	—	45	6	8	—	35
50-69 years	8	10	—	45	6	8	—	35
70+ years	8	9	—	40	6	7	—	35
Pregnant women (additional)					+1	+2	—	—
Lactating women (additional)					+3	+3	—	—

DRIs for Copper (mg/day)

Gender	Males				Females			
Age etc.	EAR	RDA	AI	UL	EAR	RDA	AI	UL
0-5 months	―	―	0.3	―	―	―	0.3	―
6-11 months	―	―	0.4	―	―	―	0.4	―
1-2 years	0.2	0.3	―	―	0.2	0.3	―	―
3-5 years	0.3	0.4	―	―	0.3	0.4	―	―
6-7 years	0.4	0.5	―	―	0.4	0.5	―	―
8-9 years	0.4	0.6	―	―	0.4	0.5	―	―
10-11 years	0.5	0.7	―	―	0.5	0.7	―	―
12-14 years	0.7	0.8	―	―	0.6	0.8	―	―
15-17 years	0.8	1.0	―	―	0.6	0.8	―	―
18-29 years	0.7	0.9	―	10	0.6	0.8	―	10
30-49 years	0.7	1.0	―	10	0.6	0.8	―	10
50-69 years	0.7	0.9	―	10	0.6	0.8	―	10
70+ years	0.7	0.9	―	10	0.6	0.7	―	10
Pregnant women (additional)					+0.1	+0.1	―	―
Lactating women (additional)					+0.5	+0.5	―	―

DRIs for Manganese (mg/day)

Gender	Males		Females	
Age etc.	AI	UL	AI	UL
0-5 months	0.01	—	0.01	—
6-11 months	0.5	—	0.5	—
1-2 years	1.5	—	1.5	—
3-5 years	1.5	—	1.5	—
6-7 years	2.0	—	2.0	—
8-9 years	2.5	—	2.5	—
10-11 years	3.0	—	3.0	—
12-14 years	4.0	—	4.0	—
15-17 years	4.5	—	3.5	—
18-29 years	4.0	11	3.5	11
30-49 years	4.0	11	3.5	11
50-69 years	4.0	11	3.5	11
70+ years	4.0	11	3.5	11
Pregnant women			3.5	—
Lactating women			3.5	—

DRIs for Iodine (μg/day)

Gender	Males				Females			
Age etc.	EAR	RDA	AI	UL	EAR	RDA	AI	UL
0-5 months	—	—	100	250	—	—	100	250
6-11 months	—	—	130	250	—	—	130	250
1-2 years	35	50	—	250	35	50	—	250
3-5 years	45	60	—	350	45	60	—	350
6-7 years	55	75	—	500	55	75	—	500
8-9 years	65	90	—	500	65	90	—	500
10-11 years	80	110	—	500	80	110	—	500
12-14 years	100	140	—	1,200	100	140	—	1,200
15-17 years	100	140	—	2,000	100	140	—	2,000
18-29 years	95	130	—	3,000	95	130	—	3,000
30-49 years	95	130	—	3,000	95	130	—	3,000
50-69 years	95	130	—	3,000	95	130	—	3,000
70+ years	95	130	—	3,000	95	130	—	3,000
Pregnant women (additional)					+75	+110	—	—[1]
Lactating women (additional)					+100	+140	—	—

[1] UL of pregnant women is determined to be 2,000 μg/day.

DRIs for Selenium (μg/day)

Gender	Males				Females			
Age etc.	EAR	RDA	AI	UL	EAR	RDA	AI	UL
0-5 months	—	—	15	—	—	—	15	—
6-11 months	—	—	15	—	—	—	15	—
1-2 years	10	10	—	80	10	10	—	70
3-5 years	10	15	—	110	10	10	—	110
6-7 years	15	15	—	150	15	15	—	150
8-9 years	15	20	—	190	15	20	—	180
10-11 years	20	25	—	240	20	25	—	240
12-14 years	25	30	—	330	25	30	—	320
15-17 years	30	35	—	400	20	25	—	350
18-29 years	25	30	—	420	20	25	—	330
30-49 years	25	30	—	460	20	25	—	350
50-69 years	25	30	—	440	20	25	—	350
70+ years	25	30	—	400	20	25	—	330
Pregnant women (additional)					+5	+5	—	—
Lactating women (additional)					+15	+20	—	—

DRIs for Chromium (μg/day)

Gender	Males	Females
Age etc.	AI	AI
0-5 months	0.8	0.8
6-11 months	1.0	1.0
1-2 years	—	—
3-5 years	—	—
6-7 years	—	—
8-9 years	—	—
10-11 years	—	—
12-14 years	—	—
15-17 years	—	—
18-29 years	10	10
30-49 years	10	10
50-69 years	10	10
70+ years	10	10
Pregnant women		10
Lactating women		10

DRIs for Molybdenum (μg/day)

Gender	Males				Females			
Age etc.	EAR	RDA	AI	UL	EAR	RDA	AI	UL
0-5 months	—	—	2	—	—	—	2	—
6-11 months	—	—	10	—	—	—	10	—
1-2 years	—	—	—	—	—	—	—	—
3-5 years	—	—	—	—	—	—	—	—
6-7 years	—	—	—	—	—	—	—	—
8-9 years	—	—	—	—	—	—	—	—
10-11 years	—	—	—	—	—	—	—	—
12-14 years	—	—	—	—	—	—	—	—
15-17 years	—	—	—	—	—	—	—	—
18-29 years	20	25	—	550	20	20	—	450
30-49 years	25	30	—	550	20	25	—	450
50-69 years	20	25	—	550	20	25	—	450
70+ years	20	25	—	550	20	20	—	450
Pregnant women (additional)					—	—	—	—
Lactating women (additional)					+3	+3	—	—

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