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Dietary Reference Intakes for Japanese 2010: Fat

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Summary In the Dietary Reference Intakes (DRIs) for fat, adequate intake (AI) and tentative dietary goal for preventing lifestyle-related disease (DGs) were used. AIs were set for *n*-6 and *n*-3 polyunsaturated fatty acids, which are essential fatty acids because they are not produced by the human body and their deficiency leads to dermatitis. DGs have been set for total fat, saturated fat, *n*-6 fatty acids, *n*-3 fatty acids, and cholesterol, whose consumption levels affect risk of lifestyle-related disease, including obesity, diabetes mellitus, cardiovascular disease, and stroke. As AI for *n*-6 and *n*-3 polyunsaturated fatty acids, the 50th percentile of *n*-6 and *n*-3 fatty acid intake was set. In the Japanese population, 98% of dietary *n*-6 fatty acids come from linoleic acid; therefore the amount of *n*-6 fatty acid intake is considered to be that of linoleic acid. Both α-linolenic (60% of total *n*-3 fatty acids) acid and fish oils are considered essential fatty acids because it has been difficult to conclude that only α-linolenic acid is essential for humans. The prevention of diabetes mellitus and stroke was emphasized. For example, an increase in saturated fatty acids intake leads to increased incidences in obesity, diabetes, and myocardial infarction, whereas a decrease of saturated fatty acids intake is associated with increased incidence in brain hemorrhage. Therefore, DG of saturated fatty acids in those more than 18 y of age was set between 4.5 and 7% energy.

Key Words total fat, saturated fat, monounsaturated fat, *n*-6 fatty acids, *n*-3 fatty acids, cholesterol, trans fatty acids

Background Information

In the Dietary Reference Intakes for Japanese (DRIs-J) 2010 for fat, the adequate intakes (AIs) and tentative dietary goal for preventing lifestyle-related disease (DGs) for fat were determined. Specifically, AIs were set for *n*-6 and *n*-3 polyunsaturated fatty acids, which are essential fatty acids because they are not produced by the human body and their deficiency leads to disease. DGs have been set for total fat, saturated fat, *n*-6 fatty acids, *n*-3 fatty acids, and cholesterol, whose consumption levels affect risk of lifestyle-related disease, including obesity, diabetes mellitus, cardiovascular disease, and stroke.

Total fatty acids, saturated fat, and *n*-6 fatty acids are major fuels that supply energy to humans. Therefore, they are expressed as percentage of energy (%en) from total energy intake. Essential fatty acids, including metabolites of α-linolenic acid are expressed as absolute values (g/d) but not relative values (en% of total energy) due to their essentiality.

To estimate the average amount of fatty acid intake in the Japanese which was used for DRIs, it was calculated using the original data that had been collected by the 2005 and 2006 NHNS. The 50th percentiles of the major fatty acids and cholesterol are presented in the original Japanese DRIs. For the determination of DGs in the DRIs-J 2010, systematic reviews were conducted by using appropriate key words in PubMed. From these publications, 437 related to DRIs were selected for careful reading and, along with those that had been used for the DRIs-J 2005, were used for a review of the DRIs-J 2010.

In this paper, the original version of the Japanese DRIs has been summarized and only selected sections discussed for the sake of brevity.

Determining DRIs

1. Total fat

1-1. DG (lower boundary). A low fat/high carbohydrate diet leads to increased postprandial glucose and fasting triacylglycerol (TG) concentrations and decreased fasting high-density lipoprotein (HDL)-cholesterol concentration (*1*). Although there is no definite evidence that average daily fat intake in a low fat/high carbohydrate diet increases risk of obesity and diabetes mellitus, unfavorable metabolite profiles in low fat/high carbohydrate diets indicate that a lower boundary of adequate total fat intake exists.

As described in the following sections, the AI of *n*-6

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Table 1. Dietary Reference Intakes for total fat [Ratio of total fat to total energy (percentage of fat energy): % energy].

Sex	Males		Females	
Age	AI	DG (range)	AI	DG (range)
0–5 mo	50	—	50	—
6–11 mo	40	—	40	—
1–2 y	—	20≤, <30	—	20≤, <30
3–5 y	—	20≤, <30	—	20≤, <30
6–7 y	—	20≤, <30	—	20≤, <30
8–9 y	—	20≤, <30	—	20≤, <30
10–11 y	—	20≤, <30	—	20≤, <30
12–14 y	—	20≤, <30	—	20≤, <30
15–17 y	—	20≤, <30	—	20≤, <30
18–29 y	—	20≤, <30	—	20≤, <30
30–49 y	—	20≤, <25	—	20≤, <25
50–69 y	—	20≤, <25	—	20≤, <25
≥70 y	—	20≤, <25	—	20≤, <25
Pregnant women			—	—
Lactating women			—	—

AI, adequate intake; DG, tentative dietary goal for preventing lifestyle-related diseases.

Table 2. Dietary Reference Intakes for saturated fatty acids (% energy).

Sex	Males	Females
Age	AI (range)	AI (range)
0–5 mo	—	—
6–11 mo	—	—
1–2 y	—	—
3–5 y	—	—
6–7 y	—	—
8–9 y	—	—
10–11 y	—	—
12–14 y	—	—
15–17 y	—	—
18–29 y	4.5≤, <7.0	4.5≤, <7.0
30–49 y	4.5≤, <7.0	4.5≤, <7.0
50–69 y	4.5≤, <7.0	4.5≤, <7.0
≥70 y	4.5≤, <7.0	4.5≤, <7.0
Pregnant women		—
Lactating women		—

AI, adequate intake.

fatty acids was set at approximately 5 en%, the AI (or DG) of *n*-3 fatty acids at approximately 1 en%, and the lower DG (lower boundary) of saturated fat at approximately 5 en%. The 50th percentile value for monounsaturated fat was found to be approximately 6 en% and the total fatty acid level was 17 en% (=5+1+5+6). Considering the glycerol portion of TG (approximately 10% of total fat), approximately 20 en% was set as the lower boundary for total fat (Table 1).

1-2. DG (upper boundary). The prevention of obesity, which leads to diabetes and other diseases, is a major concern for public health. There might be an optimal dietary fat to carbohydrate ratio for prevention and treatment of obesity. In a meta-analysis of general populations under free-living conditions, a reduction in the percentage of energy as fat was found to be positively and independently associated with weight loss (*2*). Another meta-analysis of intervention studies provided support for this conclusion (*3*). However, obese subjects with hyperinsulinemia (or insulin resistance) lost more weight on a moderately low-carbohydrate (or low-glycemic load) diet consisting of 40 en% carbohydrates and 30 to 35 en% fat than on a low-fat diet consisting of 55 to 60 en% carbohydrate and 20% fat, whereas those without hyperinsulinemia lost more weight on the low-fat diet than the moderately low-carbohydrate diet (*4–6*). The optimal dietary fat to carbohydrate ratio may differ in populations depending on the prevalence of obesity.

Considering the lower prevalence of obesity in the Japanese population, the upper boundary of total fat was set as the 50th percentile of fat en% of Japanese nationwide survey, which is 30 en% for individuals aged 1 to 29 y and 25 en% for individuals aged 30 y and over (Table 1).

2. Saturated fat

2-1. DG (lower boundary). In 3 Japanese cohort studies, subjects who ate less saturated fat showed an increased risk of hemorrhagic stroke (*7–9*). First, in the Ni-Hon-San Study, which followed males aged 45 to 69 y (n=1,366) in Hiroshima and Nagasaki for 4 y (1972 to 1976), subjects who ate less than 5 g/d of saturated fat showed an increased incidence of intracranial hemorrhage (*9*). Second, in the Honolulu Heart Program, a 10-y cohort study of male Hawaiians of Japanese descent that examined the relationship between dietary fat and cholesterol and mortality, subjects who ate less than 10 g/d of saturated fat showed a 2-fold increase in the incidence of stroke (bleeding and infarction were not identified separately) than subjects who ate more than 10 g/d of saturated fat (*8*). Third, in a 14-y prospective study (1983 to 1997) of 4,775 Japanese aged 40 to 69 y who participated in a single 24-h dietary recall survey, a low intake of saturated fat (approximately <10 g/d) was found to be associated with increased risk of intraparenchymal hemorrhage after adjusting for known cardiovascular risk factors (*7*). No study found an association between saturated fat intake and risk of brain infarction (*10*).

To determine the lower DG boundary for saturated fat, the results of 2 studies were examined. In a cohort study in Hawaii, subjects who ate less than 10 g/d (=3.9 en%) of saturated fat showed an increase in total mortality and mortality due to cancer, coronary heart disease, and stroke relative to subjects who ate more than 10 g/d of saturated fat (*8*). In a cohort study of Japanese subjects, the multivariate relative risk was found to be 3.37 for the lowest quartile (5.0 g/d), 2.60 for the second

lowest quartile (8.5 g/d), and 2.21 for the third lowest quartile (11.9 g/d=5.3 en%) compared to the highest quartile (18.3 g/d) (7). As these findings indicate that individuals who eat less than 4.6 en% (=(3.9+5.3)/2) saturated fat may have an increased risk of death and lifestyle-related diseases, the rounded value of 4.5 en% was set as the lower boundary of the DG for saturated fat for adults aged 18 y and over (Table 2). Because the amount of animal protein was not adjusted for further examination in these 2 studies, it is possible that the increase in hemorrhagic stroke observed had been due to a shortage of animal protein rather than a shortage of saturated fat. Therefore, to prevent hemorrhagic stroke, consumption of saturated fat from dairy products and animal meat is recommended.

2-2. DG (upper boundary). An increased intake of saturated fat has been hypothesized to elevate low-density lipoprotein (LDL)-cholesterol concentration and, ultimately, promote the development of atherosclerosis. However, cohort studies in the United States have not supported this hypothesis. In the Nurses' Health Study, the significantly positive association that had been found between saturated fat intake and mortality due to coronary heart disease (CHD) disappeared after adjusting for confounding factors (*11*). In a cohort of US males, the positive association that had been found between intake of saturated fat and incidence of myocardial infarction disappeared after adjusting for dietary fiber intake (*12*). However, age may affect these associations. Two studies found a positive association between intake of saturated fat and incidence of CHD for adults aged 60 y and over but not for adults aged under 60 y (*13, 14*). In contrast, several intervention studies demonstrated that reduction of saturated fat intake led to reduced incidence of ischemic heart disease, degree of atherosclerosis, and LDL-cholesterol concentration (*15–17*). In a meta-analysis to examine the effects of dietary changes on blood lipid profile, intake of less than 10 en% (National Cholesterol Education Program Step I diet) or less than 7 en% (National Cholesterol Education Program Step II diet) of saturated fat resulted in significant reductions in blood LDL-cholesterol concentrations over a period of 1 mo to 2 y (*3*).

Several cross-sectional studies showed a positive association between intake of saturated fat and prevalence of obesity (*18*). Observational studies have reported a positive association between saturated fat intake and the prevalence of diabetes, but these positive associations disappeared after adjusting for body mass index (BMI) (*19–21*). However, cross-sectional studies have reported a positive association between saturated fat intake and prevalence of insulin resistance (a cause of Type 2 diabetes) even after adjusting for BMI (*22–24*). Furthermore, intervention studies have observed a positive association between dietary saturated fat intake and insulin resistance (*25, 26*). These results indicate that increased intake of saturated fat may increase body weight and insulin resistance (independent of obesity) and eventually lead to the development of diabetes mellitus.

In summary, saturated fat intake has been associated with increased incidence of myocardial infarction, obesity, and diabetes mellitus in a dose-dependent manner. Thus, although it is not clear that increased intake of saturated fat is a cause of these diseases due to a lack of large scale intervention study, research suggests that a diet high in saturated fat may promote these diseases. A meta-analysis of intervention studies in the United States and Europe indicates that a diet of 10 en% or less saturated fat decreases LDL-cholesterol concentration by 12% while a diet of 7 en% or less saturated fat decreases in LDL-cholesterol concentration by 16% (*3*). These data indicate that lower intake of saturated fat leads to lower incidence of myocardial infarction, obesity, and diabetes mellitus.

In the Japanese population, the 50th percentile value of dietary saturated fat, which is approximately 7 en%, was set as the upper boundary of the saturated fat DG for adults (Table 2). In younger individuals, the associations between saturated fat and lifestyle-related diseases are unclear, but it has been reported that subjects whose total blood cholesterol concentrations were high at age 22 y experienced high incidence of cardiovascular disease 27 to 42 y later (*27*). Therefore, 7 en% was also set as the upper boundary for saturated fat intake for subjects aged 18 to 19 y.

3. Monounsaturated fat

3-1. DG (lower and upper boundaries). In intervention studies conducted over relatively short periods, metabolic markers (LDL-cholesterol or insulin resistance) in subjects fed a high-monounsaturated fat diet were found to be better than those fed a high-saturated fat diet or a high-carbohydrate diet. However, in diabetic subjects, a high-monounsaturated fat diet (25 en%) resulted in a greater increase in body weight than a high-carbohydrate diet (*28*). The results of long-term cohort studies are mixed, with some finding a negative association (*29*), others no association (*11*), and yet others a positive association (*13, 14, 30, 31*) between monounsaturated fat intake and incidence of CHD.

Increasing dietary monounsaturated fat may lead to obesity and atherosclerosis when total energy intake is not restricted. However, when total fat intake is below 25 to 30 en% and the lower boundary of saturated fat, *n*-6, and *n*-3 fatty acids is maintained, intake of monounsaturated fat will be below 15 to 20 en% and overconsumption of monounsaturated fat will be avoided. Therefore, lower and upper boundaries of monounsaturated fat were not set.

4. n-6 fatty acids

4-1. AI. As the human body is unable to synthesize *n*-6 fatty acids, they are classified as essential fatty acids, thus requiring that an AI be set for these lipids. However, there are no data available to elucidate the appropriate AI value in healthy Japanese. In the Japanese population, 98% of dietary *n*-6 fatty acids come from linoleic acid. Patients deficient in *n*-6 fatty acids develop dermatitis, which can be improved by supplementation of 7.4 to 8.0 g/d or 2 en% of linoleic acid. Considering that most Japanese do not suffer from diseases due to *n*-6 fatty acid deficiency, the 50th percentile

Table 3. Dietary Reference Intakes for *n*-6 fatty acids.

Sex	Males		Females	
Age	AI (g/d)	DG (% energy)	AI (g/d)	DG (% energy)
0–5 mo	4	—	4	—
6–11 mo	5	—	5	—
1–2 y	5	—	5	—
3–5 y	7	—	6	—
6–7 y	8	—	7	—
8–9 y	9	—	8	—
10–11 y	10	—	9	—
12–14 y	11	—	10	—
15–17 y	13	—	11	—
18–29 y	11	<10	9	<10
30–49 y	10	<10	9	<10
50–69 y	10	<10	8	<10
≥70 y	8	<10	7	<10
Pregnant women (amount to be added)			+1	—
Lactating women (amount to be added)			+0	—

AI, adequate intake; DG, tentative dietary goal for preventing lifestyle-related diseases.

Table 4. Dietary Reference Intakes for *n*-3 fatty acids (g/d).

Sex	Males		Females	
Age	AI	DG	AI	DG
0–5 mo	0.9	—	0.9	—
6–11 mo	0.9	—	0.9	—
1–2 y	0.9	—	0.9	—
3–5 y	1.2	—	1.2	—
6–7 y	1.6	—	1.3	—
8–9 y	1.7	—	1.5	—
10–11 y	1.8	—	1.7	—
12–14 y	2.1	—	2.1	—
15–17 y	2.5	—	2.1	—
18–29 y	—	2.1≤	—	1.8≤
30–49 y	—	2.2≤	—	1.8≤
50–69 y	—	2.4≤	—	2.1≤
≥70 y	—	2.2≤	—	1.8≤
Pregnant women			1.9	—
Lactating women			1.7	—

AI, adequate intake; DG, tentative dietary goal for preventing lifestyle-related diseases.
Note: In the DG, it is advised to have more than 1 g/d of EPA+DHA.

of *n*-6 fatty acid intake was set as the AI for *n*-6 fatty acids (Table 3).

4-2. DG (lower boundary). As there is no strong evidence that low intake of *n*-6 fatty acids increases risk of disease, a DG (lower boundary) was not set.

4-3. DG (upper boundary). Despite some concern that excessive intake of *n*-6 fatty acids may lead to increased incidence of cancer (*32*), recent meta-analyses do not support this concern (*33*, *34*). Because delta-6 desaturase competitively acts on both linoleic acid and α-linolenic acid, increased intake of linoleic acid may decrease production of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the metabolites of α-linolenic acid. However, adequate intake of EPA and DHA could counteract this unfavorable effect.

The effects of high intake of *n*-6 fatty acids (more than 10 en%) on mortality and mobility have not been studied in detail. Because linoleic acid produces inflammatory fat, such as prostaglandin and leukotriene (*35*), high intake of *n*-6 fatty acids could be a risk to health. Indeed, a recent Japanese cross-sectional study of school children found that the odds ratio of the prevalence of wheezing for the highest quintile of intake (14.5 g/d) was 1.2 (95% CI, 1.06 to 1.37) relative to the lowest quintile (5.7 g/d) (*36*).

Although there is no definite evidence that high intake of *n*-6 fatty acids is a risk factor, an upper boundary was set at 10 en% for adults in recognition of the possible association between high intake and chronic inflammation (Table 3).

5. n-3 fatty acids

5-1. Background information. Dietary *n*-3 fatty acids are primarily found in 2 sources: vegetable oil, which contains α-linolenic acid, and fish oil, which contains EPA, DHA, and docosahexaenoic acid (DPA). A portion of α-linolenic acid is metabolized to EPA and DHA in humans and 59% of total *n*-3 fatty acid in diet is in the form of α-linolenic acid, as well as that DHA intake is 1.8-fold larger than EPA intake and that DPA intake is only 30% of EPA intake. Moreover, according to a Japanese nationwide survey, there are marked differences between the 50th percentile median and mean values of EPA, DPA, and DHA intake, with the former approximately half the latter (data not shown). Therefore, it is uncertain whether the 50th percentile values of fish oil intake are a good index of the average amount of fish oil intake by a population.

Because the beneficial physiological effects of *n*-3 fatty acids might be due to the direct effects of *n*-3 fatty acids rather than their metabolic competition with *n*-6 fatty acids, the ratio of *n*-3/*n*-6 fatty acids was not used to set the DRIs for *n*-3 fatty acids. Epidemiologic observations support this notion. In the Nurses' Health Study, the inverse association that had been found between α-linolenic acid and risk of coronary artery disease (CAD) was not affected by linoleic acid intake (*37*). In the Health Professional Study, the inverse association that had been found between α-linolenic acid or EPA and DHA intake and risk of coronary artery disease was not confounded by linoleic acid intake (*38*).

5-2. AI. Since *n*-3 fatty acids are essential fatty acids, an AI for *n*-3 fatty acid intake should be set. Because administering both α-linolenic acid and fish oil to patients deficient in *n*-3 fatty acids has been found

to result in improvement of dermatitis and increase in body weight (*39*), it has been difficult to conclude that only α-linolenic acid is essential for humans. Therefore, all *n*-3 fatty acids, including both α-linolenic acid and fish oils, are considered essential fatty acids. Although there are no data with which to elucidate the appropriate AI value for healthy Japanese, the 50th percentile of *n*-3 fatty acid intake was set as the AI in consideration of the fact that most Japanese do not suffer from diseases due to *n*-3 fatty acid deficiency (Table 4).

5-3. DG (lower boundary) of a-linolenic acid. Intervention studies in France and India identified 1.8 g/d as the intake of α-linolenic acid that reduces the mortality of patients with CHD (*40, 41*). The Iowa Women's Health Study, a prospective cohort study of postmenopausal women, found an inverse association between intake of α-linolenic acid and total mortality (*42*). Several cohort studies have shown an inverse association between intake of α-linolenic acid and incidence of CHD in the United States (*12, 37, 43*). Recognizing that these favorable effects may apply to the Japanese population, intake of α-linolenic acid for adults aged 18 y and over is advised to be equal to or higher than the current 50th percentile values of the Japanese population (in men, 50th percentile values of α-linolenic acid are 1.49 (in 18–29 y old), 1.42 (30–49 y old), 1.32 (50–69 y old) and 1.06 g/d (70 y old and over), respectively, and in women, 1.24 (in 18–29 y old), 1.19 (30–49 y old), 1.14 (50–69 y old) and 0.96 g/d (70 y old and over), respectively).

5-4. DG (upper boundary) of a-linolenic acid. A long-term intervention study in Japanese elderly subjects showed that an increase of 3.0 g/d of α-linolenic acid (total intake of α-linolenic acid of 4.8 g/d) had no adverse effects on lipid profiles or major metabolites in blood (*44*). Although the DG (upper boundary) of α-linolenic acid was not set, large habitual intake of α-linolenic acid in males should be avoided due to concern that it may increase the incidence of prostate cancer (*45*).

5-5. DG (lower boundary) of EPA and DHA. Many studies have found a positive association between intake of *n*-3 fatty acids and reduced risk of CAD (*46*). A recent review that examined the association between the intake of EPA and DHA and mortality due to CAD identified a threshold of EPA and DHA intake—0.5 g/d—above which no further reduction in CAD mortality resulted (*47*). Likewise, clinical studies have identified a threshold of 0.75 g/d for reducing blood pressure and risk of arrhythmia (*47*). However, no threshold regarding intake and nonfatal coronary events has been identified in Japanese subjects. In a Japanese cohort study (the JPHC Study), the multivariable hazard ratio of nonfatal coronary events of the highest quintile (EPA and DHA intake of 2.1 g/d) was found to be 67% lower than that of the lowest quintile (EPA and DHA intake of 0.3 g/d) (*48*), while the hazard ratio of the middle quintile (EPA and DHA intake of 0.9 g/d) was found to decrease significantly (39%). In the Japan Eicosapentaenoic Acid Lipid Intervention Study (the JELIS), in which 18,645 patients with a total cholesterol of 250 mg/dL or greater were randomly assigned to receive 1.8 g/d EPA with statins or statins only, a 19% relative reduction in major coronary events was observed in the EPA with statins group over a 5-y follow-up period (*49*). However, this reduction was only observed regarding unstable angina, not coronary death.

The findings of other studies indicate that EPA and DHA intake may reduce the incidence of heart failure. In a Japanese cohort study (the JACC Study), the hazard ratio for the highest quintile (EPA, DHA, and DPA intake of 2.11 to 5.06 g/d) was found to be 0.58 (95% CI, 0.36 to 0.93) relative to the lowest quintile (EPA, DHA, and DPA intake of 0.05 to 1.18 g/d) (*50*). In an intervention study in Italy, supplementation of 1 g/d of EPA and DHA significantly reduced risk of death and rate of hospital re-admission for heart failure patients (*51*), while several US studies have found an inverse association between fish intake and the incidence of brain infarction (*52–54*). The JELIS found that supplementation of 1.8 g/d of EPA decreased the relative risk of stroke recurrence by 20% (*55*). Other studies have found an inverse association between EPA and DHA intake and incidence of age-related macular degeneration (*56–58*), as well as that high EPA+DHA intake has favorable effects on allergic rhinitis (*59*), peak bone mineral density (*60*), and aged-induced cognitive decline (*61, 62*).

These findings indicate that high EPA and DHA intake could reduce the incidence of CAD, stroke, and age-related macular degeneration. One study found that Japanese subjects whose average intake of EPA and DHA was 0.9 g/d showed a significant reduction in hazard ratio (0.61; 95% CI, 0.38 to 0.98) for nonfatal cardiac events compared subjects whose intake was 0.3 g/d (*48*). Rounding this value (0.9 g/d), the DG for the lower boundary of EPA and DHA was set at 1 g/d, which is equivalent to approximately 90 g/d of fish (Table 4).

5-6. DG (upper boundary) of EPA and DHA. The possible adverse effects of EPA and DHA intake on bleeding time, LDL-cholesterol concentration, blood glucose level, immune functions, lipid peroxide level, and plasminogen activator inhibitor-1 (PAI-1) have been reviewed systematically (*46*). Intake at typical daily levels has not been found to result in increased occurrence of clinically significant adverse effects (*46*). In the JELIS, administration of 1.8 g/d EPA did not increase hemorrhagic stroke, stomach cancer, lung cancer, colon cancer, breast cancer, or LDL-cholesterol concentration (*49*). Therefore, a DG (upper boundary) of EPA and DHA was not set.

In setting the DRIs, the safety of incidental intake of heavy metals, such as mercury, cadmium, lead, and tin, and of chemical environmental pollutants, such as dioxins and polychlorinated biphenyls (PCBs), which are generally present in fish, was not considered because other regulations apply to these compounds. In addition, the amount of toxic compounds varies between fish species and the areas where fish are caught. Guidelines for the safety of toxic compounds in food have been issued by the Japanese Government and should also be referred to.

Table 5. Dietary Reference Intakes for cholesterol (mg/d).

Sex	Males	Females
Age	DG	DG
0–5 mo	—	—
6–11 mo	—	—
1–2 y	—	—
3–5 y	—	—
6–7 y	—	—
8–9 y	—	—
10–11 y	—	—
12–14 y	—	—
15–17 y	—	—
18–29 y	<750	<600
30–49 y	<750	<600
50–69 y	<750	<600
≥70 y	<750	<600
Pregnant women		—
Lactating women		—

DG, tentative dietary goal for preventing lifestyle-related diseases.

5-7. DG (lower and upper boundary) of n-3 fatty acids. Questions such as "If sufficient amounts of EPA and DHA are consumed, is it unnecessary to consume α-linolenic acid?" and "When very low amounts of EPA and DHA are consumed, should intake of α-linolenic acid be increased ?" are difficult to answer because of insufficient data regarding the optimal ratio of α-linolenic acid to EPA and DHA intake. Therefore, the DG (lower boundary) of total *n*-3 fatty acid intake (including α-linolenic acid, EPA, and DHA) for adults aged 18 y and over was set at the 50th percentile value of the dietary intake of the Japanese population. However, as both the JPHC study and the JELIS observed beneficial effects of fish oil intake on CAD (albeit without considering basal intake of α-linolenic acid), more than 1 g/d intake of EPA and DHA is advised, regardless of intake of α-linolenic acid. A DG for the upper boundary of total *n*-3 fatty acids was not set because the values for α-linolenic acid and fish oils were not set (Table 4).

6. Dietary cholesterol

6-1. DG (lower boundary). Either increased or decreased blood cholesterol concentration has been associated with elevated mortality from stroke in a U-shaped-curve manner (*63*). The increased mortality from ischemic stroke observed in subjects with high blood cholesterol concentrations was due in part to increased LDL-cholesterol concentration, which promotes atherosclerosis. Observation of elevated mortality from intracerebral hemorrhage in patients with lower blood cholesterol concentrations does not confirm that low blood cholesterol concentration is a cause of hemorrhagic stroke (*64, 65*). Japanese cohort studies have found no association between dietary cholesterol intake and incidence of stroke, including hemorrhagic stroke (*7, 8, 10, 66*). Interestingly, one study that had identified an inverse association between dietary cholesterol intake and incidence of stroke found that this association disappeared after adjusting for intake of animal protein and fat (*66*). As a meta-analysis found that treatment to reduce blood cholesterol concentration did not increase incidence of stroke (*67*), a DG (lower boundary) for cholesterol was not set.

6-2. DG (upper boundary). In cohort studies in the United States, no association was found between intake of cholesterol (or egg consumption) and incidence of CAD (*12, 68–70*). However, in the Honolulu Heart Program Study, Japanese whose intake of cholesterol was more than 325 mg/1,000 kcal (747 mg/d expressed on a daily basis), showed a significant increase in mortality from CHD (*8*). In one of the NIPPON DATA 80 studies, a series of cohort studies conducted in Japan, no association was found between egg consumption and death due to ischemic heart disease in subjects who had undergone dietary assessment in 1980 and been followed up to 1994 (*71*). In a study in which subjects underwent dietary assessment between 1990 and 1994 and were followed up to 2001, those who ate fewer eggs were found to have increased incidence of CHD (*72*). However, this finding could be attributed to reverse causation; that is, the subjects with high blood cholesterol tended to reduce egg consumption due to exposure to a public campaign advising them to do so to lower their blood cholesterol. Therefore, it is difficult to interpret the results of recent studies that examined the association between cholesterol intake and cardiovascular disease. In the NIPPON DATA 80 study, women who ate more than 2 eggs per day were found to have a 2-fold higher risk of mortality from cancer compared with women who seldom ate eggs (*71*). Recent studies have supported this finding, having found a positive association between intake of cholesterol and incidence of ovarian and endometrial cancer (*73, 74*) as well as lung, pancreatic, and colon/rectal cancer (*75*). Thus, a high intake of cholesterol is not recommended for the public at large. Using the data from the Honolulu Heart Program Study (*8*), the DG for the upper boundary of cholesterol intake was set at 750 mg/d for men and 600 mg/d for women, with these different values reflecting adjustment by differences in daily energy intake (Table 5).

7. Trans fatty acids

7-1. Background information. Trans fatty acids are mostly derived from 3 sources: 1) partially hydrogenated foods, such as margarine; 2) geometrical isomers of linoleic and α-linolenic acid resulting from the deodorization process; and 3) naturally occurring trans fatty acids from beef, lamb, and dairy fat resulting from biohydrogenation in ruminants. In humans, high intake of partially hydrogenated vegetable oils has been associated with increased incidence of CHD, obesity, allergies, lower birth weight, and fetal loss (*76*). As high intake of trans fatty acids derived from ruminants has not been associated with CHD, obesity, or diabetes, it is considered less harmful than high intake of other forms of trans fatty acids (*77–80*).

7-2. DG (upper boundary). High intake of trans

fatty acids leads to an increase in blood LDL-cholesterol and a decrease in HDL-cholesterol concentration, resulting in an increase in the LDL-cholesterol/HDL-cholesterol and total cholesterol/HDL-cholesterol ratios in a dose-dependent manner (*8*). High intake of trans fatty acids has also been associated with increased risk of CHD in a dose-dependent manner (*11*). However, it is unclear whether the incidence of CHD is significantly higher among average Japanese adults, who consume a low amount of trans fatty acids, than it is among Japanese adults who consume no trans fatty acids at all. Nevertheless, it is conceivable that in individuals with multiple risk factors for CHD, such as smoking, hypertension, diabetes mellitus, and dyslipidemia, increased intake of trans fatty acids may promote atherosclerosis to a greater degree than in individuals without these risk factors. Increased intake of trans fatty acids may increase the incidence of several diseases, such as CHD, obesity, and allergies and result in lower birth weight and increased risk of fetal loss, especially in individuals with other risk factors. Therefore, it is recommended that we eat less trans fatty acids at all ages.

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Dietary Reference Intakes for Japanese 2010: Carbohydrates

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Summary The Dietary Reference Intakes (DRIs) of carbohydrates and dietary fiber were determined for Japanese. The estimated average requirement (EAR) and recommended dietary allowance (RDA) for carbohydrates were not determined because of insufficient data. The tentative dietary goal for preventing lifestyle-related diseases (DG) for children aged 1 y and above was determined for carbohydrates (% energy). In addition, the DG for adults aged 18 y and above was determined for dietary fiber. Dietary fiber intake is associated with myocardial infarction; therefore, the DG was determined on the basis of the results of a meta-analysis and the median dietary fiber intake of Japanese. The DG for alcohol was not determined because of insufficient data.

Key Words carbohydrate, dietary fibers, alcohol, lifestyle-related diseases

Introduction

A carbohydrate comprises either a monosaccharide or its polymer (*1*). Carbohydrates play an important nutritional role as an energy source; digestible carbohydrates (i.e., sugars and starches) contain approximately 4 kcal of energy/g. Although there is no internationally standardized definition, dietary fiber is usually considered an indigestible component in the diet, many of which are carbohydrates. Indigestible carbohydrates are fermented by intestinal bacteria, theoretically providing 0–2 kcal/g (*2*). Dietary fiber is an important nutrient, not as an energy source, but because of its relationship with lifestyle-related diseases attributable to physiological functioning.

Alcohol was included in this chapter considering that it has several effects on health and affects nutritional status and energy production.

Carbohydrates

Basic concept

The primary role of carbohydrates is to supply glucose to tissues that can ordinarily only use glucose as an energy source, such as the brain, nervous tissue, red blood cells, renal tubules, the testes, and oxygen-deficient skeletal muscle. It is estimated that the daily glucose requirement of these tissues is at least 100 g/d (*3*); however, this value is not the true minimal glucose requirement, because gluconeogenesis occurs in the liver. According to the National Health and Nutrition Survey in Japan (*4*, *5*), almost all Japanese consume the minimum requirement.

The dietary goal for preventing lifestyle-related diseases (DG) for carbohydrates was determined as the difference between the energy derived from proteins and lipids and the estimated energy requirement (EER), provided that sufficient proteins and a suitable amount of lipids are being ingested. Thus, the DG of carbohydrates is expressed as a percentage of energy. Since the indigestible carbohydrates in ordinary diets have almost no energy, they are considered to be carbohydrates. Furthermore, the energy derived from carbohydrates is not strongly influenced if the energy derived from ordinary amounts of alcohol consumption is included (*6*). However, this does not mean that alcohol can be used as a substitute for carbohydrates.

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Table 1. Dietary Reference Intakes for carbohydrates (% energy).[1]

Sex	Males	Females
Age	DG (range)	DG (range)
0–5 mo	—	—
6–11 mo	—	—
1–2 y	50≤, <70	50≤, <70
3–5 y	50≤, <70	50≤, <70
6–7 y	50≤, <70	50≤, <70
8–9 y	50≤, <70	50≤, <70
10–11 y	50≤, <70	50≤, <70
12–14 y	50≤, <70	50≤, <70
15–17 y	50≤, <70	50≤, <70
18–29 y	50≤, <70	50≤, <70
30–49 y	50≤, <70	50≤, <70
50–69 y	50≤, <70	50≤, <70
≥70 y	50≤, <70	50≤, <70
Pregnant women (amount to be added)		—
Lactating women (amount to be added)		—

DG, tentative dietary goal for preventing lifestyle-related diseases.

[1] Including energy derived from alcohol.

Table 2. Dietary Reference Intakes for dietary fibers (g/d).

Sex	Males	Females
Age	DG	DG
0–5 mo	—	—
6–11 mo	—	—
1–2 y	—	—
3–5 y	—	—
6–7 y	—	—
8–9 y	—	—
10–11 y	—	—
12–14 y	—	—
15–17 y	—	—
18–29 y	≥19	≥17
30–49 y	≥19	≥17
50–69 y	≥19	≥17
≥70 y	≥19	≥17
Pregnant women (amount to be added)		—
Lactating women (amount to be added)		—

DG, tentative dietary goal for preventing lifestyle-related diseases.

Determining the Dietary Reference Intakes

DG (Tentative dietary goal for preventing lifestyle-related diseases)

Adults/children. The DG for carbohydrates was determined for children aged 1 y and above. The DG was determined according to the intake of carbohydrates (60–72% energy), assuming that the subject is consuming their EER (physical activity level II), lipids within the DG, and the recommended dietary allowance (RDA) of protein. Although a lack of sufficient evidence, considering cases in which a person's protein intake is greater than the RDA and that EER differs with respect to physical activity level, the DGs for adults and children were set at 50–70% of energy intake.

DRIs values for carbohydrates are listed in Table 1.

Dietary fiber

Basic concept

Dietary fiber intake is associated with various lifestyle-related diseases. Many studies report negative relationships between dietary fiber intake and the incidence of myocardial infarction, myocardial infarction-related deaths (*7*), the incidence of diabetes (*8*), blood pressure (*9*), and low-density lipoprotein cholesterol (*10*). There are also many reports showing a correlation between dietary fiber intake and obesity (*11*, *12*). However, the associations between dietary fiber intake and cancer and its effect on bowel habits (e.g., constipation) are not well identified (*13*, *14*).

The lifestyle-related disease with the clearest connection to dietary fiber intake is myocardial infarction (*7*). Therefore, the DG was determined on the basis of the results of a meta-analysis (*7*) as well as the current intake levels of dietary fiber in Japanese.

Determining the Dietary Reference Intakes

Tentative dietary goal for preventing lifestyle-related diseases

Adults. The results of a meta-analysis of the correlation between dietary fiber intake and myocardial infarction revealed that the mortality rate decreases with a daily intake level of at least 24 g/d and increases with a daily intake level less than 12 g/d (*7*). According to the National Health and Nutrition Surveys Japan in 2005 and 2006 (*4*, *5*), the median dietary fiber intakes of male and female adults are 12.3–16.3 and 11.8–16.1 g/d, respectively.

The DG for dietary fiber was determined on the basis of the intermediate value (i.e., 18 g/d) between the 2 values indicated in the meta-analysis (*7*) although a lack of scientific basis. Furthermore, taking into account the age and body weight of the research subjects and the difference in standard body weight between Japanese men and women, the DG was determined to be 19 and 17 g/d for men and women, respectively.

DRIs values for dietary fiber are listed in Table 2.

Alcohol

Basic concept

In Japan, 7.1 kcal/g is used as the amount of available energy from alcohol (ethanol) (*15*, *16*). However, the energy utilization efficiency of alcohol varies according

to a variety of conditions including alcohol consumption levels, the ability to metabolize alcohol, dietary intake levels, and physical condition.

The range of "moderate alcohol consumption" (*17*) is thought to be in the order of 20 g/d pure alcohol equivalent. In this range, there would be no problem using 7.1 kcal/g to calculate the amount of energy from the perspective of maintaining body weight.

Epidemiological studies show that alcohol intake is correlated with death and the incidence of cardiovascular disease, cancer, and other lifestyle-related diseases (*18–21*). Western and Japanese have very different genetic backgrounds with respect to the metabolic enzymes of alcohol (*22*). Thus, it is possible that the health effects of alcohol in Japanese are different from those in Western people. The exact level of alcoholic intake that affects the total mortality rate is still controversial among cohort studies in Japan. Some studies report that the risk of mortality is lowest among subjects who consume less than 21 g alcohol/d (*23*), while others report that the risk is only high with a consumption of more than 43 g/d (*24*). Furthermore, other reports indicate that the risk increases gradually with increasing alcohol consumption (*25*). However, in all cases, it is clear that heavy alcohol consumption increases the risk of mortality.

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Dietary Reference Intakes for Japanese 2010: Fat-Soluble Vitamins

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Summary We have determined the Dietary Reference Intakes for fat-soluble vitamins (vitamin A, vitamin D, vitamin E, and vitamin K) for the Japanese. Regarding vitamin A, the estimated average requirement (EAR) and the recommended dietary allowance (RDA) were defined for those aged 1 y old and over. For vitamin D, vitamin E, and vitamin K, the EAR or RDA was not adopted, because of the insufficient data available. Thus, the adequate intake (AI) was determined for those vitamins based on the food surveillance data and biomarkers for each vitamin. The AI for vitamin D was decided as the median intake of vitamin D in the population with a circulating 25-hydroxy vitamin D level which was high enough for bone health. The basis for the AI for vitamin E was the median intake of α-tocopherol in the healthy population considering the lack of unfavorable health consequences attributable to its deficiency. The AI for vitamin K was determined as the vitamin K intake, required to avoid blood coagulation abnormalities. The tolerable upper intake level (UL) was determined for vitamin A, vitamin D and vitamin E, but not for vitamin K, since no adverse effects have been reported even with its high dosage.

Key Words vitamin A, vitamin D, vitamin E, vitamin K

Vitamin A

Background information

Compounds with potent vitamin A activity in vivo after oral intake include retinol; retinal; carotenoids; and 50 different types of provitamin A carotenoids, including β-carotene, α-carotene, and β-cryptoxanthin. The retinol equivalent (RE) is the vitamin A unit used in Dietary Reference Intakes for Japanese (DRIs-J) 2010, the most current Dietary Reference Intakes (DRIs) for the Japanese. Retinoic acid, a hormone binding to the nuclear receptor, is responsible for the majority of vitamin A activity in vivo, but is not converted to retinal or retinol in vivo, and its content in food is relatively low. Retinylester provitamin A carotenoids are the main forms of vitamin A contained in animal and plant foods, respectively. Retinylester hydrolase in the intestinal brush border catalyzes the hydrolysis of retinylester to retinol, which is then absorbed at a rate that ranges from 70% to 90% (*1*, *2*). Cleavage of carotenoids yields 2 molecules of vitamin A (retinal) from β-carotene (*3*) and 1 molecule from other provitamin A carotenoids.

In the DRIs-J 2010, the absorption rate of β-carotene is 1/6 of its total value, which is in accordance with rate in the DRIs for the United States and Canada (*4*). Assuming that the conversion rate of β-carotene to retinol is 50%, the bioavailability of β-carotene as vitamin A is 1/12 (1/6×1/2), such that 12 μg of food-derived β-carotene would correspond to 1 μg in RE units. Thus, the following formula can be used to convert the value of food-derived vitamin A-related compounds into RE units:

Retinol equivalent (μg RE)
=retinol (μg)+β-carotene (μg)×1/12
+α-carotene (μg)×1/24+β-cryptoxantin (μg)
×1/24+other provitamin A carotenoids (μg)
×1/24.

A word of caution is indicated when calculating the value for oil-solubilized β-carotene, as its bioavailability as a form of vitamin A is 1/2 of its total value, such that 2 μg of fat-solubilized β-carotene would correspond to 1 μg of retinol.

Determining DRIs

Classical vitamin A deficiency leads to corneal xerosis in infants and possibly to blindness and to night blindness in adults. Other deficiency signs include growth retardation; skeletal and neurological development defects; disturbed growth and differentiation of epi-

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thelial cells; dryness, thickening, and keratinization of the skin; immunodeficiency; and susceptibility to infection (*5*). Due to the abundant storage of vitamin A in the liver, inadequate intake does not lead to decreased plasma retinol concentration unless hepatic vitamin A storage is below 20 μg/g (*6*, *7*). Thus, plasma retinol concentration cannot be used as an index of vitamin A status. Theoretically, hepatic vitamin A storage is the best index, but its measurement is highly invasive and not applicable to humans. Thus, the vitamin A intake required to maintain minimal hepatic vitamin A storage has been used for estimating the Estimated Average Requirement (EAR) for vitamin A.

Compartment analysis assuming the existence of 3 compartments—serum, liver, and other tissues—has shown that the daily disposal rate of vitamin A is approximately 2% (*8*, *9*). Using this percentage, the daily disposal amount (DDA), daily disposal rate (DDR), body storage (BS) according to body weight (BW), and hepatic storage (HS) of vitamin A can be calculated as follows:

DDA (μg/d)=BS (μg)×DDR (2%/d (*10*)).

BS/BW (μg/kg BW)

=HS (≥20 μg/g)×liver weight/BW (21 g/kg BW) ×10/9,

where 90% of the body storage of vitamin A is in the liver (*10*, *11*).

DDA/BW (μg/[kg BW·d])

=BS (≥20 μg/g×21 g/kg×10/9)×DDR (2/100)

=9.3 μg/kg BW.

Thus, the amount of vitamin A intake required to compensate for its daily elimination, thereby ensuring that hepatic storage of vitamin A is maintained and vitamin A deficiency is avoided, is estimated to be 9.3 μg RE/kg BW/d.

EAR and Recommended Dietary Allowance (RDA) for adults

The EAR for vitamin A for those aged 18 y and above, as calculated by multiplication of the reference value of 9.3 μg RE/kg BW/d and the reference BW, is 550 to 600 μg RE/d for males and 450 to 500 μg RE/d for females. Assuming the inter-individual variability in vitamin A requirement to be 20% (*4*), multiplication of these EAR values by 1.4 yields an RDA of 800 to 850 μg RE/d for males and 650 to 700 μg RE/d for females.

EAR and RDA for children

The RDA for children aged 6 to 17 y was determined by extrapolation from the EAR for adults aged 18 to 29 y by the 0.75th power of the BW ratio, which represents the ratio of body surface area (*4*). Extrapolation of the adult EAR to preschool children based on BW ratio may yield values that maintain plasma retinol levels below 20 μg/100 mL, and thus render children susceptible to corneal xerosis (*12*). Therefore, the RDA for children aged less than 5 y must be at least 200 μg RE/d to avoid this unfavorable outcome; therefore, for children aged less than 5 y, the DDA was calculated as follows, assuming the ratio of liver weight/BW to be 42 g/kg BW (*10*):

DDA/BW (μg/kg BW/d)

=BS (≥20 μg/g×42 g/kg×10/9)×DDR (2/100)

=18.7 μg/kg BW.

Using the value obtained, the EAR for children aged 1 to 5 y was calculated as follows:

EAR=18.7 μg/kg BW/d×reference BW×(1+growth factor)

=EAR×1.4.

Adequate Intake of infants aged 0 to 5 mo

Vitamin A concentration in breast milk is highest during the first 10 d after delivery, after which it gradually decreases (*13*, *14*). Based on the values for average vitamin A concentration (411 μg RE/L) (*14*) and daily milk intake (0.78 L/d) (*15*, *16*), vitamin A intake in breast milk-fed infants aged 0 to 5 mo was estimated at 320 μg RE/d. Thus, adequate intake (AI) for this age group was determined to be 300 μg/d. The level of provitamin A carotenoids was not taken into account because its availability is unknown.

AI of infants 6 to 11 mo

Based on extrapolation from the AI for infants aged 0 to 5 mo, the AI for infants aged 6 to 11 mo was determined to be 400 μg RE/d. The level of provitamin A carotenoids was not taken into account because its availability is unknown.

Amount to be added during pregnancy

The amount of vitamin A transported to the fetus through the placenta must be taken into account when estimating the vitamin A requirement for pregnant women. At the late-stage of a fetus, the amount of vitamin A deposited in the fetal liver was 1,800 μg (*17*, *18*) so that the total amount of vitamin A transported to the fetus during pregnancy is estimated at 3,600 μg. Using this value, the EAR value for the additional amount of vitamin A required during the late stage was determined to be 60 μg RE/d, which, assuming an inter-individual variability of 20% (*4*), yielded an RDA value of 80 μg RE/d during the late-stage. The additional amount required during the early- and mid-stage was not determined.

Amount to be added during lactation

Based on measurement of the amount of vitamin A secreted in breast milk, the EAR value for the additional amount of vitamin A required during lactation was estimated at 300 μg RE/d, which, assuming an inter-individual variability of 20%, yielded an RDA value of 450 μg RE/d (*4*).

Tolerable upper intake level

An elevated plasma level of retinoic acid is considered responsible for most clinical signs (*19*) and symptoms of vitamin A intoxication, such as headache. Based on reported fetal abnormalities due to excessive intake of vitamin A, (*20*, *21*) the no observable adverse effect level (NOAEL) during pregnancy was estimated at 4,500 μg RE/d, which, assuming an uncertainty factor of 1.5 and taking the additional amount into account, yielded an upper level (UL) of 3,000 μg RE/d.

Based on research into hepatotoxicity caused by the excessive vitamin A deposition (*22*), the NOAEL in adults was estimated at 13,500 μg RE/d, which, assuming an uncertainty factor of 5, yielded a UL of 2,700 μg RE/d. Based on clinical observation of increased intracranial pressure in infants caused by excessive vitamin

Table 1. DRIs for vitamin A (μg RE/d).[1]

Sex	Males				Females			
Age	EAR[2]	RDA[2]	AI[3]	UL[3]	EAR[2]	RDA[2]	AI[3]	UL[3]
0–5 mo	—	—	300	600	—	—	300	600
6–11 mo	—	—	400	600	—	—	400	600
1–2 y	300	400	—	600	250	350	—	600
3–5 y	300	450	—	700	300	450	—	700
6–7 y	300	450	—	900	300	400	—	900
8–9 y	350	500	—	1,200	350	500	—	1,200
10–11 y	450	600	—	1,500	400	550	—	1,500
12–14 y	550	750	—	2,000	500	700	—	2,000
15–17 y	650	900	—	2,500	450	650	—	2,500
18–29 y	600	850	—	2,700	450	650	—	2,700
30–49 y	600	850	—	2,700	500	700	—	2,700
50–69 y	600	850	—	2,700	500	700	—	2,700
≥70 y	550	800	—	2,700	450	650	—	2,700
Pregnant women (amount to be added)								
Early-stage					+0	+0	—	—
Mid-stage					+0	+0	—	—
Late-stage					+60	+80	—	—
Lactating women (amount to be added)					+300	+450	—	—

DRIs, Dietary Reference Intakes; RE, retinol equivalents; EAR, estimated average requirement; RDA, recommended dietary allowance; AI, adequate intake; UL, tolerable upper intake level.

[1] Retinol equivalent (μg RE)=retinol (μg)+β-carotene (μg)×1/12+α-carotene (μg)×1/24+β-cryptoxanthin (μg)×1/24 +other provitamin A carotenoids (μg)×1/24.

[2] Including provitamin A carotenoids.

[3] Excluding provitamin A carotenoids.

A intake (*23*), the NOAEL in infants was estimated at 6,000 μg RE/d, which, assuming an uncertainty factor of 10, yielded a UL of 600 μg RE/d.

The UL for children aged 1 to 17 y was determined by extrapolation from the UL for adults based on the ratio of body surface area. For safety reasons, the values for men were applied to women. Extrapolation to infants aged 1 to 2 y old yielded a UL of 500 μg RE/d, which is lower than that for infants aged 6 to 11 mo (600 μg RE/d). Thus, the UL for infants aged 1 to 2 y old was revised to 600 μg RE/d. Although a recent study found that ingesting approximately 1,500 μg RE/d of retinol for 30 y doubled the fracture risk in the elderly (*24*), data from other studies contradicted this finding. Thus, determination of a separate UL for vitamin A for the elderly was not considered in developing the most recent DRIs. Moreover, as excessive intake of β-carotene has not been reported to be associated with the unfavorable consequences of vitamin A intoxication described above, the level of provitamin A carotenoids was also not included in the estimation of UL.

Remarks regarding carotenoids

Due to the strict regulation of their conversion into vitamin A, provitamin A carotenoids, when ingested orally, cannot cause vitamin A intoxication. Unconverted provitamin A carotenoids, as well as carotenoids that are not metabolized to vitamin A are stored in vivo as they are. Beneficial actions have been reported with ingestion of these carotenoids, including anti-oxidant activity and immune potentiation and photoprotection of skin by anti-oxidation. Regarding the benefits of specific carotenoids, prevention of prostate cancer by lycopene, improvement in age-related macular degeneration by lutein and zeaxanthin, and the maintenance of retinal pigment by lutein and zeaxanthin have also been reported. Although the results of cohort studies suggest that higher intake of carotenoids is associated with lower incidence of lung cancer (*25*), supplementary intervention has been reported to be ineffective or even harmful in the prevention of cancer, especially lung cancer (*26–29*). Thus, further research into the efficacy and safety of carotenoids is required. In developing the current DRIs, the carotenoids were not separately considered because their deficiency has not been reported.

DRI values for vitamin A are listed in Table 1.

Vitamin D

Background information

Vitamin D_2 and vitamin D_3 are naturally occurring compounds with potent vitamin D activity. The indices for the DRI of vitamin D is based on the summation of the values of these 2 compounds. The human body obtains vitamin D from 2 sources. One is exposure to ultraviolet irradiation, which converts pro-vitamin D_3

(7-dehydrocholesterol) in the skin to pre-vitamin D_3, which in turn is converted into vitamin D_3 by thermal isomerization. The other is dietary intake of vitamin D_2 and vitamin D_3 from such sources as mushrooms and fish; good sources for vitamin D_2 and vitamin D_3, respectively. The current DRIs do not discriminate between vitamin D_2 and D_3 intake because the compounds have similar characteristics and a similar molecular weight and exert an almost equal level of biological activity.

Vitamin D is first metabolized to 25-hydroxy vitamin D (25OHD) before being metabolized to 1α,25-dihydroxy vitamin D ($1\alpha,25(OH)_2D$), its active form. Major actions of vitamin D include enhancing the absorption of calcium and phosphate in the intestine and kidneys and stimulating bone formation and growth. Circulating 25OHD level is the best index of vitamin D status. As vitamin D deficiency and resultant hypocalcemia cause elevated levels of serum parathyroid hormone (PTH), serum concentration of PTH can also be a good index of vitamin D deficiency (*30*).

Adequate intake

Evidence for determining AI

Vitamin D deficiency impairs calcium absorption from the intestine and kidney, thus decreases calcium availability, resulting in rickets in children and osteomalacia in adults. In adults, especially the elderly, even so-called "vitamin D insufficiency," which is milder than vitamin D deficiency, can result in increased secretion of PTH, increased bone resorption, and decreased bone mineral density. Therefore, the basis for determining the vitamin D requirement is maintenance of a serum 25OHD level sufficiently high to maintain normal calcium availability and avoid elevation of serum PTH level. Due to limitations on the data available, AI was determined as the median intake of vitamin D in a population in which the required circulating 25OHD level is maintained.

AI for adults

In a study conducted in the northern United States, an area in which residents receive limited sunshine exposure, serum PTH level after vitamin D administration decreased in those with a serum 25OHD level below 50 nmol/L but not in those with a level above 50 nmol/L (*31*). In a study in Niigata, those with a 25OHD level less than 50 nmol/L had higher serum PTH levels and a higher prevalence of low bone mineral density (*32*). Based on consideration of these results, maintenance of a circulating 25OHD level of at least 50 nmol/L is considered necessary to avoid elevation of serum PTH level and decrease in bone mineral density. In the study conducted in the northern United States, serum PTH level exhibited seasonal variation, reaching a nadir between August and October and a peak between March and May. However, this variation was not observed in those taking 5.5 μg/d or more of vitamin D (*33*), leading to the conclusion that taking at least 5.5 μg/d of vitamin D can prevent elevation of PTH in those living in areas in which they have limited sunshine exposure.

In 7 studies that examined Japanese women (*34–39*) aged 50 to 69 y, the average 25OHD level was found to exceed 50 nmol/L. In contrast, in several studies that examined women aged 18 to 29 y (*32*, *34*) and women aged 30 to 49 y (*34*), the average level was found to be below 50 nmol/L. Based on these findings and the findings from US studies, the median vitamin D intake of adults aged 50 to 69 y was determined to be an appropriate basis for determining the adult AI. As the 2005 and 2006 National Health and Nutritional Survey (NHNS) (*40*, *41*) found that the median intake of vitamin D in adults aged 50 to 69 y was 5.5 μg/d, the AI was set as 5.5 μg/d. Due to lack of data for those aged 18 to 29 y, 30 to 49 y, and above 70 y, as well as lack of data for males, AI for both males and females in these age groups was also set at 5.5 μg/d.

AI for children

As the findings regarding the relationship between vitamin D intake and plasma 25OHD concentration in children have been inconsistent, they were considered unsuitable as the basis for determining the vitamin D AI for children. Thus, the median vitamin D intake, as reported in the 2005 and 2006 NHNS (*40*, *41*), was used as the basis for determining the AI.

AI for infants

In an epidemiological study conducted in Kyoto, 22% of neonates were found to have craniotabes, a mineralization defect of bone, likely due to vitamin D deficiency (*42*). The incidence of craniotabes exhibited seasonal variation, with a peak and nadir between January and May and between July and November, respectively. Circulating 25OHD level was found to be below 25 nmol/L in 37% of all neonates diagnosed with craniotabes at 1 mo after birth. In breast milk-fed neonates, serum concentration of 25OHD was found to be less than 25 nmol/L in 57% of subjects and below 12.5 nmol/L in 17%. In contrast, none of the formula or mixed-fed infants were found to have an inadequate serum 25OHD level. It should be noted that neonates born in a vitamin D-deficient state may not recover to a vitamin D-sufficient state within a short period, and that the serum 25OHD level of breast milk-fed infants was found to decrease further during the winter months (*43*), indicating that the vitamin D delivered from breast milk may have been unsatisfactory. The vitamin D AI for infants was determined to be 2.5 μg/d by multiplying 0.78 L/d (*15*, *16*), the average daily milk intake, by 3.05 μg/L (*44*), the vitamin D concentration in breast milk as reported in the *Standard Tables of Food Composition in Japan*, 5th Revised and Enlarged Edition.

However, this AI value is appropriate only for infants with adequate sun exposure, defined as 2 h/wk to the face or 30 min/wk to the face and extremities. Breast-milk-fed infants with little sun exposure are at higher risk of developing rickets. Considering that previous research found that no infants developed rickets after supplementation with 2.5 μg/d of vitamin D for 6 mo and assuming that infants receive an average of 2.38 μg/d of vitamin D from breast milk, it follows that a daily intake of 4.88 μg/d of vitamin D is satisfactory for avoiding rickets. Based on these data, the AI of vitamin D for infants aged 0 to 5 mo with limited sun exposure was determined to be 5 μg/d. Recently, however, a

Table 2. DRIs for vitamin D (μg/d).

Sex	Males				Females			
Age	EAR	RDA	AI	UL	EAR	RDA	AI	UL
0–5 mo[1]	—	—	2.5 (5.0)	25	—	—	2.5 (5.0)	25
6–11 mo[1]	—	—	5.0 (5.0)	25	—	—	5.0 (5.0)	25
1–2 y	—	—	2.5	25	—	—	2.5	25
3–5 y	—	—	2.5	30	—	—	2.5	30
6–7 y	—	—	2.5	30	—	—	2.5	30
8–9 y	—	—	3.0	35	—	—	3.0	35
10–11 y	—	—	3.5	35	—	—	3.5	35
12–14 y	—	—	3.5	45	—	—	3.5	45
15–17 y	—	—	4.5	50	—	—	4.5	50
18–29 y	—	—	5.5	50	—	—	5.5	50
30–49 y	—	—	5.5	50	—	—	5.5	50
50–69 y	—	—	5.5	50	—	—	5.5	50
≥70 y	—	—	5.5	50	—	—	5.5	50
Pregnant women (amount to be added)					—	—	+1.5	—
Lactating women (amount to be added)					—	—	+2.5	—

[1] Adequate intakes for an infant who is exposed to appropriate sunlight. The value in parentheses is adequate intakes for those with less sunlight exposure.

study using a novel, highly accurate procedure found the average vitamin D concentration in breast milk to be only 0.6 μg/L (*14*). If this value is employed, the average vitamin D intake of breast-milk-fed infants would be only 0.47 μg/d. Such discrepancies indicate the need for further research into this value (*45*, *46*).

AI for infants aged 6 to 11 mo

The AI of vitamin D for infants aged 6 to 11 mo with adequate sun exposure was determined to be 5 μg/d. This value was also applied to infants aged 6 to 11 mo with limited sun exposure due to lack of evidence for determining the AI.

Additional amount during pregnancy

In a study of pregnant women with limited sun exposure, an inadequate serum 25OHD concentration was observed in those with an average vitamin D intake of less than 5.3 μg/d but not in those an average (*47*) vitamin D intake higher than 7 μg/d (*48*). As these findings indicate that pregnant women require at least 7 μg/d of vitamin D, the additional amount of vitamin D required for pregnant women was determined to be 1.5 μg/d.

Additional amount during lactation

Based on the findings described above, the additional amount of vitamin D required for lactating women was determined to be 2.5 μg/d.

Tolerable upper untake level

Basic considerations

Prolonged intake of excessive quantities of vitamin D can lead to unfavorable outcomes, such as hypercalcemia, renal dysfunction, soft tissue calcification, and growth retardation. As an increased serum 25OHD level itself does not directly cause health problems, the presence of hypercalcemia rather than of a high serum 25OHD level is considered an appropriate indicator for determining the UL.

UL for adults

In an intervention study administering doses of vitamin D for 3 mo, serum calcium concentration was found to exceed the reference value in some subjects receiving 95 μg/d of vitamin D but not in those receiving 60 μg/d of vitamin D (*49*). Thus, the lowest observed adverse effect level (LOAEL) and NOAEL were determined to be 95 μg/d and 60 μg/d, respectively. The latter value was divided by an uncertainty factor of 1.2 yielding a UL for adults of 50 μg/d. Since neither administration of 45 μg/d of vitamin D to elderly subjects for 3 mo (*50*) nor administration of 50 μg/d to pregnant and lactating subjects (*51*) was found to be associated with hypercalcemia, stratification by sex or age group was not performed, and a UL of 50 μg/d was applied to all adult groups.

UL for infants

Based on a study that observed no growth retardation in infants administered an average of 44 μg/d of vitamin D for 6 mo, the NOAEL for infants was determined to be 44 μg/d (*52*), which, assuming an uncertainty factor of 1.8, yielded a UL of 25 μg/d.

UL for children

As data were unavailable for this age group, the UL for children was determined by extrapolating the UL values for adults (50 μg/d) and infants (25 μg/d) based on the reference body weight. Sex differences were not considered.

DRI values for vitamin D are listed in Table 2.

Vitamin E

Background information

Vitamin E is composed of 8 analogues: α-, β-, γ- and

Table 3. DRIs for vitamin E (mg/d).[1]

Sex	Males				Females			
Age	EAR	RDA	AI	UL	EAR	RDA	AI	UL
0–5 mo	—	—	3.0	—	—	—	3.0	—
6–11 mo	—	—	3.5	—	—	—	3.5	—
1–2 y	—	—	3.5	150	—	—	3.5	150
3–5 y	—	—	4.5	200	—	—	4.5	200
6–7 y	—	—	5.0	300	—	—	5.0	300
8–9 y	—	—	6.0	350	—	—	5.5	350
10–11 y	—	—	6.5	450	—	—	6.0	450
12–14 y	—	—	7.0	600	—	—	7.0	600
15–17 y	—	—	8.0	750	—	—	7.0	650
18–29 y	—	—	7.0	800	—	—	6.5	650
30–49 y	—	—	7.0	900	—	—	6.5	700
50–69 y	—	—	7.0	850	—	—	6.5	700
≥70 y	—	—	7.0	750	—	—	6.5	650
Pregnant women (amount to be added)					—	—	+0.0	—
Lactating women (amount to be added)					—	—	+3.0	—

[1] *Computation was made on α-tocopherol, not including vitamins E other than α-tocopherol.*

δ-forms, of tocopherol and tocotrienol. After intestinal absorption, vitamin E is packaged into chylomicron, transformed into chylomicron remnant by lipoprotein lipase, and transported to the liver. Of the 8 analogues, only α-tocopherol is preferentially bound to α-tocopherol binding protein, whereas the other analogues are metabolized in the liver. Alpha-tocopherol is then formed into very low-density lipoprotein (VLDL), converted into low-density lipoprotein (LDL), and distributed to various tissues (*53*). Due to these metabolic processes, α-tocopherol constitutes the predominant vitamin E analogues present in the blood and various tissues. Based on these facts, only α-tocopherol was considered when determining the current DRI for vitamin E.

Determining DRI

Basis for determining AI

Erythrocytes are susceptible to hemolysis by hydrogen peroxide when the circulating α-tocopherol level is between 6 and 12 μmol/L (*54*), but resistant to it when the serum α-tocopherol level is higher than 14 μmol/L (*55*). Although the data from an intervention study that administered graded doses of vitamin E to vitamin E-deficient subjects are available (*56*), they were not considered appropriate for estimating the EAR and RDA because they were collected many years ago. Several studies that simultaneously studied vitamin E intake and serum α-tocopherol level consistently reported that the average serum α-tocopherol level exceeded 22 μmol/L in all study populations (*40, 41, 57–59*). Average vitamin E intake in these studies ranged from 5.6 to 11.1 mg/d, a range that encompasses the 2005 and 2006 NHNS values (*40, 41*) of an average vitamin E intake of 7.0 mg/d in men and 6.5 mg/d in women. As these findings indicate that the median intake of the Japanese likely yields an adequate vitamin E status, the AI was determined to be the 2005 and 2006 NHNS median values stratified by sex and age group (*40, 41*).

AI for adults

As described above, AI was determined to be the 2005 and 2006 NHNS median values for those aged 18 to 29 y stratified by sex and age group, specifically 7.0 mg/d for men and 6.5 mg/d for women, as these values are expected to yield a blood α-tocopherol level exceeding 12 μmol/L (*40, 41*). As aging has not been reported to be associated with compromised absorption or utilization of vitamin E, the same values were applied to the elderly.

AI for children

The 2005 and 2006 NHNS median values for children stratified by sex and age group were used as the basis for determining the AI for children, as they had been for adults.

AI for infants aged 0 to 5 mo

The AI for infants aged 0 to 5 mo was determined to be 3.0 mg/d by multiplying the average α-tocopherol concentration in breast milk (3.5 to 4.0 mg/L) (*14, 60*) by the average milk intake (0.78 L/d) (*15, 16*).

AI for infants aged 6 to 11 mo

The AI for infants aged 6 to 11 mo old was determined to be 3.5 mg/d by extrapolation from the adult value by the 0.75th power of the BW ratio.

AI during pregnancy

The AI for pregnant women was determined to be the same as that for non-pregnant women because vitamin E deficiency during pregnancy has not been reported.

Additional amount during lactation

Since the average α-tocopherol content provided in breast milk is approximately 3.0 mg/d (*14, 60*), the AI