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 ($1/6 \times 1/2$), 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:

$$\begin{aligned} &\text{Retinol equivalent } (\mu\text{g RE}) \\ &= \text{retinol } (\mu\text{g}) + \beta\text{-carotene } (\mu\text{g}) \times 1/12 \\ &\quad + \alpha\text{-carotene } (\mu\text{g}) \times 1/24 + \beta\text{-cryptoxanthin } (\mu\text{g}) \\ &\quad \times 1/24 + \text{other provitamin A carotenoids } (\mu\text{g}) \\ &\quad \times 1/24. \end{aligned}$$

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 $\mu\text{g/g}$ (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:

$$\text{DDA } (\mu\text{g/d}) = \text{BS } (\mu\text{g}) \times \text{DDR } (2\%/d \text{ (10)}).$$

$$\text{BS/BW } (\mu\text{g/kg BW})$$

$$= \text{HS } (\geq 20 \mu\text{g/g}) \times \text{liver weight/BW } (21 \text{ g/kg BW}) \times 10/9,$$

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

$$\text{DDA/BW } (\mu\text{g}/[\text{kg BW} \cdot \text{d}])$$

$$= \text{BS } (\geq 20 \mu\text{g/g} \times 21 \text{ g/kg} \times 10/9) \times \text{DDR } (2/100)$$

$$= 9.3 \mu\text{g/kg BW}.$$

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 $\mu\text{g RE/kg BW/d}$.

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 $\mu\text{g RE/kg BW/d}$ and the reference BW, is 550 to 600 $\mu\text{g RE/d}$ for males and 450 to 500 $\mu\text{g RE/d}$ 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 $\mu\text{g RE/d}$ for males and 650 to 700 $\mu\text{g RE/d}$ 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 $\mu\text{g}/100 \text{ mL}$, and thus render children susceptible to corneal xerosis (12). Therefore, the RDA for children aged less than 5 y must be at least 200 $\mu\text{g RE/d}$ 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):

$$\text{DDA/BW } (\mu\text{g/kg BW/d})$$

$$= \text{BS } (\geq 20 \mu\text{g/g} \times 42 \text{ g/kg} \times 10/9) \times \text{DDR } (2/100)$$

$$= 18.7 \mu\text{g/kg BW}.$$

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

$$\text{EAR} = 18.7 \mu\text{g/kg BW/d} \times \text{reference BW} \times (1 + \text{growth factor})$$

$$= \text{EAR} \times 1.4.$$

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 $\mu\text{g RE/L}$) (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 $\mu\text{g RE/d}$. Thus, adequate intake (AI) for this age group was determined to be 300 $\mu\text{g/d}$. 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 $\mu\text{g RE/d}$. 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 $\mu\text{g RE/d}$, which, assuming an inter-individual variability of 20% (4), yielded an RDA value of 80 $\mu\text{g RE/d}$ 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 $\mu\text{g RE/d}$, which, assuming an inter-individual variability of 20%, yielded an RDA value of 450 $\mu\text{g RE/d}$ (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 $\mu\text{g RE/d}$, which, assuming an uncertainty factor of 1.5 and taking the additional amount into account, yielded an upper level (UL) of 3,000 $\mu\text{g RE/d}$.

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

Table 1. DRIs for vitamin A ($\mu\text{g RE/d}$).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 ($\mu\text{g RE}$) = retinol (μg) + β -carotene (μg) $\times$ 1/12 + α -carotene (μg) $\times$ 1/24 + β -cryptoxanthin (μg) $\times$ 1/24 + other provitamin A carotenoids (μg) $\times$ 1/24.

² Including provitamin A carotenoids.

³ Excluding provitamin A carotenoids.

A intake (23), the NOAEL in infants was estimated at 6,000 $\mu\text{g RE/d}$, which, assuming an uncertainty factor of 10, yielded a UL of 600 $\mu\text{g RE/d}$.

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 $\mu\text{g RE/d}$, which is lower than that for infants aged 6 to 11 mo (600 $\mu\text{g RE/d}$). Thus, the UL for infants aged 1 to 2 y old was revised to 600 $\mu\text{g RE/d}$. Although a recent study found that ingesting approximately 1,500 $\mu\text{g RE/d}$ 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 D₂ and vitamin D₃ 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 D₃

(7-dehydrocholesterol) in the skin to pre-vitamin D₃, which in turn is converted into vitamin D₃ by thermal isomerization. The other is dietary intake of vitamin D₂ and vitamin D₃ from such sources as mushrooms and fish; good sources for vitamin D₂ and vitamin D₃, respectively. The current DRIs do not discriminate between vitamin D₂ and D₃ 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 1 α ,25-dihydroxy vitamin D (1 α ,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 μ g/d or more of vitamin D (33), leading to the conclusion that taking at least 5.5 μ g/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 μ g/d, the AI was set as 5.5 μ g/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 μ g/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 μ g/d by multiplying 0.78 L/d (15, 16), the average daily milk intake, by 3.05 μ g/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 μ g/d of vitamin D for 6 mo and assuming that infants receive an average of 2.38 μ g/d of vitamin D from breast milk, it follows that a daily intake of 4.88 μ g/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 μ g/d. Recently, however, a

Table 2. DRIs for vitamin D ($\mu\text{g}/\text{d}$).

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 $\mu\text{g}/\text{L}$ (14). If this value is employed, the average vitamin D intake of breast-milk-fed infants would be only 0.47 $\mu\text{g}/\text{d}$. 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 $\mu\text{g}/\text{d}$. 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 $\mu\text{g}/\text{d}$ but not in those an average (47) vitamin D intake higher than 7 $\mu\text{g}/\text{d}$ (48). As these findings indicate that pregnant women require at least 7 $\mu\text{g}/\text{d}$ of vitamin D, the additional amount of vitamin D required for pregnant women was determined to be 1.5 $\mu\text{g}/\text{d}$.

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 $\mu\text{g}/\text{d}$.

Tolerable upper intake 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 $\mu\text{g}/\text{d}$ of vitamin D but not in those receiving 60 $\mu\text{g}/\text{d}$ of vitamin D (49). Thus, the lowest observed adverse effect level (LOAEL) and NOAEL were determined to be 95 $\mu\text{g}/\text{d}$ and 60 $\mu\text{g}/\text{d}$, respectively. The latter value was divided by an uncertainty factor of 1.2 yielding a UL for adults of 50 $\mu\text{g}/\text{d}$. Since neither administration of 45 $\mu\text{g}/\text{d}$ of vitamin D to elderly subjects for 3 mo (50) nor administration of 50 $\mu\text{g}/\text{d}$ 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 $\mu\text{g}/\text{d}$ 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 $\mu\text{g}/\text{d}$ of vitamin D for 6 mo, the NOAEL for infants was determined to be 44 $\mu\text{g}/\text{d}$ (52), which, assuming an uncertainty factor of 1.8, yielded a UL of 25 $\mu\text{g}/\text{d}$.

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 $\mu\text{g}/\text{d}$) and infants (25 $\mu\text{g}/\text{d}$) 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 $\mu\text{mol/L}$ (54), but resistant to it when the serum α -tocopherol level is higher than 14 $\mu\text{mol/L}$ (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 $\mu\text{mol/L}$ 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 $\mu\text{mol/L}$ (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

during lactation was determined to be 3 mg/d.

Tolerable upper intake level

The basis for determining the UL for vitamin E is its possible effect on bleeding tendency. Based on the finding that supplementation with 800 mg/d of α -tocopherol for 28 d did not increase bleeding tendency in healthy males (average body weight, 62.2 kg) (61), the NOAEL was determined to be 800 mg/d. Assuming an uncertainty factor of 1.0 and considering that no data regarding LOAEL are available, the sex- and age-group stratified UL was calculated by correcting the 800 mg/d value by BW ratio. Because few data are available regarding the UL for infants aged 0 to 11 mo and because typical feeding with breast milk or baby food does not cause excessive intake, the UL was not determined for this age group.

Additional remarks

Although numerous intervention studies have examined the effect of vitamin E supplementation on the risk of coronary heart diseases, the findings have been inconsistent (62–65).

DRI values for vitamin E are listed in Table 3.

Vitamin K

Basic considerations

Naturally occurring vitamin K consists of phyloquinones (PKs; vitamin K₁) and menaquinones (MKs; vitamin K₂). Menaquinones are further subdivided into 11 analogues depending on the number of isoprene units (4–14) in the prenyl side chain. Among the menaquinones, of nutritional importance are menaquinone-4 (MK-4), which is ubiquitously present in animal foods, and menaquinone-7 (MK-7), which is abundantly present in natto, a traditional Japanese food made from soybeans fermented with *Bacillus subtilis*. At present, data are scarce for determining the relative biological activity of these analogues, and no corrections have been made for PK and MK-4 with similar molecular weights. MK-7, which has a much larger molecular weight, can be converted into its MK-4 equivalent using the following formula:

$$\text{MK-4 equivalent (mg)} = \text{MK-7 (mg)} \times 444.7/649.$$

The sum of the quantity of PK, MK-4, and MK-7 as corrected above was employed in determining the DRI for vitamin K. Although long-chain MKs are produced by intestinal bacteria and MK-4 is also produced by enzymatic conversion from PK, their contribution was not considered sufficiently large to contribute to fulfilling this requirement. Although antibiotic treatment can impair vitamin K status by decreasing the production of MKs by intestinal flora and decreasing vitamin K utilization by inhibiting the enzymatic activity of vitamin K epoxide reductase (66), antibiotic treatment itself does not cause vitamin K deficiency if average vitamin K intake is maintained (67).

The principal biological action of vitamin K is activation of prothrombin and other serum coagulation factors, thereby enhancing blood coagulation. Other actions include the modulation of bone formation by activation of osteocalcin, a bone matrix protein, and

inhibition of arterial calcification by activation of matrix gla protein (MGP), another vitamin-K-dependent matrix protein.

Determining DRI

Evidence for determining AI

Since delayed blood coagulation is the only clinically manifested abnormality attributable to vitamin K deficiency, the intake necessary to maintain normal serum coagulation was considered an appropriate basis for determining the AI for vitamin K. In Japan, however, coagulation abnormalities due to vitamin K deficiency are rarely observed in healthy subjects. An intervention study of young vitamin K-deficient male volunteers weighing 72 kg found that administration of 40 and 32 $\mu\text{g/d}$ of vitamin resulted in a decrease in serum PK level and an elevation in undercarboxylated prothrombin, a serum marker for vitamin K deficiency, respectively, but that administration of 82 $\mu\text{g/d}$ of vitamin K returned these levels to normal values (68). Based on these findings, the vitamin K requirement for healthy adults was determined to be approximately 1 $\mu\text{g}/[\text{kg}\cdot\text{d}]$.

Recent studies have suggested that skeletal vitamin K deficiency is a risk factor for fracture (69, 70), indicating that a much higher vitamin K intake is necessary for skeletal action. Although a recent meta-analysis found that vitamin K administration significantly reduced fracture incidence, it employed a high dosage (45 mg/d) of MK-4, which is considered to be pharmacological rather than nutritional (71). Based on the findings of previous research, a vitamin K intake of approximately 1.0 $\mu\text{g}/[\text{kg}\cdot\text{d}]$ was determined to be satisfactory to avoid even mild deficiency, and thus set as the AI for vitamin K.

AI for adults

As described above, a vitamin K intake of 82 $\mu\text{g/d}$ in those weighing 72 kg was found sufficient to avoid deficiency (68). Extrapolation of this value by the 0.75th power of the BW ratio was used as the basis for determining the adult AI. Although the elderly may be more susceptible to vitamin K deficiency due to various factors such as impaired intestinal absorption of vitamin K, at present, the data are scarce, and thus the AI for the elderly was the same as that for those aged 50 to 69 y.

AI for children

The AI for children was determined by extrapolating the AI for adults by the 0.75th power of the BW ratio.

AI for infants aged 0 to 5 mo

Neonates are susceptible to vitamin K deficiency for various reasons, such as poor transplacental vitamin K transport (72), low vitamin K content in the breast milk (14, 73), or low production of vitamin K in the intestinal flora (74). As neonatal vitamin K deficiency is known to cause neonatal melena, a form of gastrointestinal bleeding, and intracranial bleeding, vitamin K is orally administered just after birth for their prevention. The AI of 4.0 $\mu\text{g/d}$ for this age group was determined by multiplying the average milk intake (0.78 L/d) by the average vitamin K content of milk (5.17 $\mu\text{g/L}$) and assuming oral administration of vitamin K just after birth in the clinical setting.

Table 4. DRIs for Vitamin K ($\mu\text{g}/\text{d}$).

Sex	Males				Females			
Age	EAR	RDA	AI	UL	EAR	RDA	AI	UL
0–5 mo	—	—	4	—	—	—	4	—
6–11 mo	—	—	7	—	—	—	7	—
1–2 y	—	—	25	—	—	—	25	—
3–5 y	—	—	30	—	—	—	30	—
6–7 y	—	—	40	—	—	—	40	—
8–9 y	—	—	45	—	—	—	45	—
10–11 y	—	—	55	—	—	—	55	—
12–14 y	—	—	70	—	—	—	65	—
15–17 y	—	—	80	—	—	—	60	—
18–29 y	—	—	75	—	—	—	60	—
30–49 y	—	—	75	—	—	—	65	—
50–69 y	—	—	75	—	—	—	65	—
≥ 70 y	—	—	75	—	—	—	65	—
Pregnant women (amount to be added)					—	—	+0	—
Lactating women (amount to be added)					—	—	+0	—

AI for infants aged 6 to 11 mo

The AI was determined to be 7 $\mu\text{g}/\text{d}$ by considering the amount of vitamin K received from sources other than breast milk.

Additional amount during pregnancy

Increased requirements for vitamin K or alterations in circulating vitamin K levels in pregnant women have not been reported. Because of poor transplacental transport, vitamin K intake in pregnant women is unlikely to affect vitamin K status in the fetuses or neonates. Thus, no additional amount required for pregnant women was determined.

Additional amount during lactation

Since lactating women have not been reported to be at higher risk for vitamin K deficiency, no additional amount required for lactating women was determined.

Tolerable upper intake level

Although menadione, a vitamin K metabolite, can cause toxicity, no toxicity has been reported regarding PKs and MKs. As 45 mg/d of MK-4 is clinically administered to many patients in Japan with osteoporosis with no reports of serious adverse events, the UL for vitamin K was not determined.

Other remarks

Due to the abundant vitamin K content of natto, its intake is contraindicated in patients treated with warfarin. In contrast, patients undergoing long-term antibiotic treatment or experiencing chronic obstruction of the biliary tract or impaired fat absorption are at higher risk of vitamin K deficiency.

DRI values for vitamin K are listed in Table 4.

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