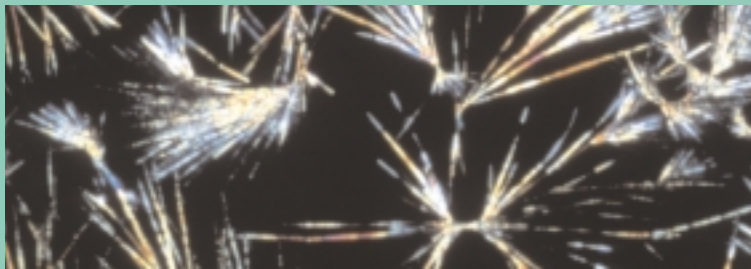
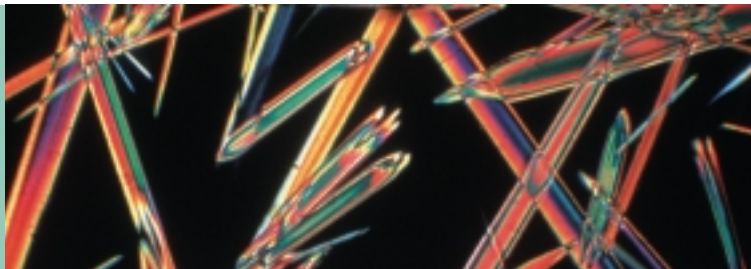


Vitamins A, D, K

Dietary Reference Intakes DRI (US Food and Nutrition Board)



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A Summary of the Panel Reports

This summary covers vitamins A, D, and K and is based on the respective US FNB Panel reports (1,2).

These reports have been elaborated by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride, and its Panel on Trace Elements, Vitamins A and K, and the Subcommittee on Upper Reference Levels of Nutrients, US Food Nutrition Board (FNB) with active involvement of Health Canada. It establishes a set of science-based reference values for the vitamins A, D, and K to replace the previously published Recommended Dietary Allowances (RDAs) for the USA and the Recommended Nutrient Intakes (RNIs) for Canada.

1. Definition and scope of Dietary Reference Intakes (DRI)

DRIs are reference values that are quantitative estimates of nutrient intakes to be used for planning and assessing diets for healthy people. They include a set of up to four values:

Estimated Average Requirement EAR: a daily nutrient intake value that is estimated to meet the requirement of half the healthy *individuals* in a group.

Recommended Dietary Allowance RDA: the average daily dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 %) healthy *individuals* in a particular life stage (age, pregnancy, lactation) and gender group.

Adequate Intake AI: a recommended daily intake value based on observed or experimentally determined approximations of nutrient intake by a *group (or groups)* of healthy people that are assumed to be adequate. The AI is a goal for the nutrient intake of *individuals*.

Tolerable Upper Intake Level UL: the highest level of daily nutrient intake that is likely to pose *no risk of adverse health effects* to almost all *individuals* in the general population. As intake increases above the UL, the risk of adverse effects increases.



General procedure to set Dietary Reference Intakes

The *Recommended Dietary Allowance RDA* is being mathematically derived from the Estimated Average Requirement EAR under consideration of the variability in requirement. Is the standard deviation SD of the EAR available and the requirement for the particular nutrient is normally distributed the

$$\mathbf{RDA = EAR + 2 SD_{EAR}}$$

If data are insufficient with regard to variability of requirement (which is mostly the case for the vitamins) an estimated coefficient of variation for the EAR of usually 10 percent is assumed and the

$$\mathbf{RDA = 1.2 \times EAR}$$

The *Estimated Average Requirement EAR* as the basis for calculating the RDA is being set following a careful review of the available scientific data base and the selection of *one specific criterion of adequacy* chosen for each of the nutrients. This includes the scientific evaluation of the data base for many health parameters as well as contemporary concepts of the reduction of disease risk.

In case sufficient scientific evidence is not available to derive an Estimated Average Requirement EAR and thus a RDA cannot be calculated, an *Adequate Intake AI* is set instead of a RDA. The AI can be considered as a surrogate of the RDA.

Tolerable Upper Intake Levels for Nutrients UL have been evaluated due to the increased interest and availability of fortified food and increased use of dietary supplements. ULs are based on total chronic

daily intake of a nutrient from food, fortified foods, and supplements. If adverse effects have been associated with intakes from food supplements or fortified foods *only*, the UL is based on nutrient intake from those sources only, and not on total intake. The UL is developed to be applied to almost all individuals in the general healthy population including sensitive individuals. The UL is not meant to apply to individuals who are treated with the respective nutrient under medical supervision.

The ULs are being derived by applying the framework of risk assessment adopted for nutrients. Risk assessment is a systematic means of evaluating the probability of occurrence of adverse health effects in humans from excess exposure to an environmental agent, in this particular case, a nutrient. The steps of risk assessment as applied to nutrients are:

- hazard identification: determination of adverse health effects caused by high intakes of the nutrient.
- dose response assessment: determines the relationship between nutrient intake/dose and adverse effect (incidence and severity). The derivation of a UL is based on the use of scientific judgement to select the appropriate no-observed-adverse-effect level (NOAEL) for the chosen adverse health effect. The NOAEL is the highest intake of a nutrient at which no adverse effects have been observed. In case, available data are inadequate to demonstrate a NOAEL, the lowest-observed-adverse-effect level (LOAEL) may be used. The LOAEL is the lowest dose at which an adverse effect



could be identified. The UL is preferentially derived from the NOAEL (or the LOAEL) by introduction of an uncertainty factor UF which deals with uncertainties in data (methodology, design of studies, analytical determination procedures, extrapolation from experimental animal data to humans, lack of data on chronic exposure, etc) and with incomplete knowledge regarding expected variability in response within the population. The UFs for nutrients are typically between 1-10, and they are lower with higher-quality data and when adverse effects are extremely mild and reversible. Thus, in general the UL is being derived by dividing the NOAEL by a single UF that incorporates all relevant uncertainties. If there are no data available on adverse effects no UL is being set.

$$UL = NOAEL / UF_1 \quad \text{or} \quad UL = LOAEL / UF_2$$

with $UF_2 > UF_1$

For specific age groups such as infants and children due to lack of data ULs were determined by extrapolating from the UL for adults (if there is one) based on body weight differences.

- Intake assessment: evaluates the range and the distribution of overall intakes of the nutrient for the population. If the UL only pertains to supplements, the assessment is directed to intake from supplements only.
- Risk characterization: estimates the risk of the fraction of the population, if any, with chronic intakes greater than the UL and evaluates the degree of excess intake exceeding the UL.

The risk assessment does not make any recommendations for reducing a potential risk; these are the tasks of risk management (government; regulatory authorities).

2. Application and use of Dietary Reference Intakes (DRI)

DRI and Intake

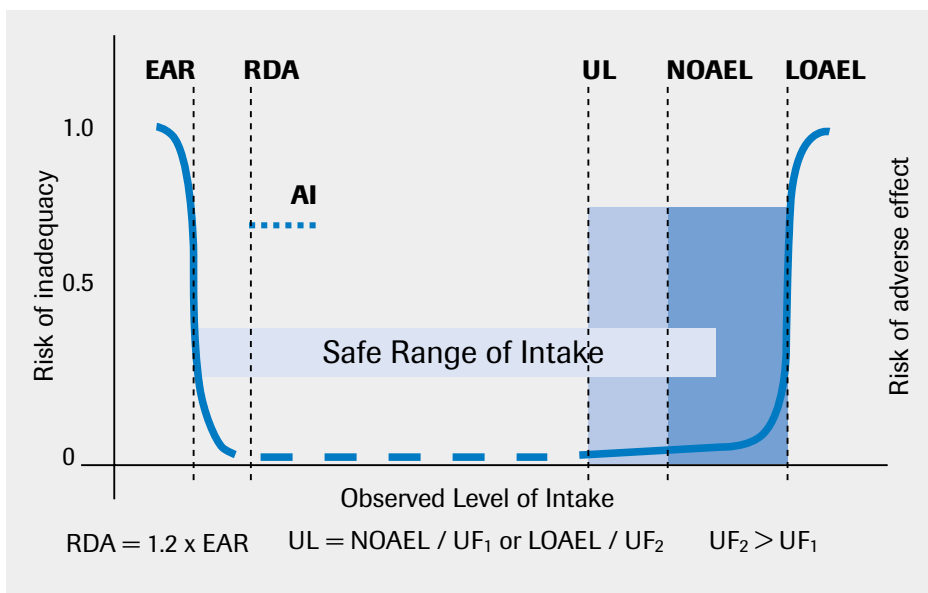


Fig.1: Dietary Reference Intakes (EAR; RDA; AI; UL), no-observed-adverse-effect (NOAEL) and lowest-observed-adverse-effect (LOAEL) intake levels. The Estimated Average Requirement (EAR) is the intake at which the risk of inadequacy is 0.5 (50%) to an individual. The Recommended Dietary Allowance (RDA) is the intake at which the risk of inadequacy is very small (about 2-3 %). At intakes between the RDA and the Tolerable Upper Level of Intake (UL) the risks of inadequacy and of excess are both close to zero. Above the UL and the NOAEL the risk of adverse effects gradually increase.

In the past, Recommended Dietary Allowances (RDAs) were the only values available to health professionals for planning and assessment of diets for individuals and groups and for making judgements on excessive intake. The newly developed Dietary Reference Intakes (DRI) are considered a more complete set of values and each value of the DRIs has a specific use. A separate Committee within the DRI process at the US Food and Nutrition Board, Institute of Medicine, is dealing with these aspects. A first report is now available and is dealing with «Application of Dietary Reference Intakes in Dietary Assessment» (3). The report dealing with the Utilization of Dietary Reference Intakes in Planning of Diets will be available by end 2001/early 2002. The general use of Dietary Reference Intakes for healthy individuals and groups is summarized below.

Use of DRIs for Planning of Diets

For the Individual

RDA: aim for this intake

AI: use as guide for intake in absence of a RDA

UL: use as guide that higher intakes may increase risk of adverse effects

For a Group

EAR: used in a way that approx 2-3% of the group have a lower intake than the group mean of requirement (EAR)

AI: use for formulation of tentative goals for mean intake of a specific population group

UL: use to ensure that goals for mean intakes of a specific population group do not place an individual in this group at risk of adverse health effects due to overconsumption

Fig 2: Uses of Dietary Reference Intakes for groups of healthy individuals

3. Criteria used for estimating the requirement

Use of DRIs for Assessment of Diets

For the Individual

EAR: use to examine the possibility of nutrient inadequacy; evaluation of true status requires biochemical, clinical, and/or anthropometric data

UL: use to examine the possibility of overconsumption and risk of adverse effects

For a Group

EAR: use in the assessment of prevalence of inadequate intakes within a group

In addition to the use of DRIs in planning and assessing of diets, these scientifically derived values will also be considered as basis of the so-called labeling RDAs (Daily Reference Values DRV) which will be determined by the regulatory bodies, in the USA by the FDA.

The establishment of DRIs follows these methodological steps: definition and selection of the nutrients to be assessed; selection and validation of indicators to be used; assessment of efficacy, and finally setting the DRIs, starting with the Estimated Average Requirement. There is a large number of factors which could possibly influence the determination of requirement:

- physiological factors (gender, age, body size and composition)
- health status (pregnancy, lactation, diabetes, asthma, chronic infections)
- life style (smoking, dieting, alcohol consumption)
- occupational factors
- environmental conditions (ambient temperature, altitude, UV exposure)
- genetic / biological variations (specific phenotypes of enzymes)

The indicators considered and the respective indicator(s) finally used for the assessment of the Estimated Average Requirement (EAR) are summarized for vitamins A, D, and K (Table I):

Table I: Vitamins A, D, and K: Indicators evaluated and actually used for the assessment of Estimated Average Requirements (EAR). (Calcium, phosphorus, magnesium, vitamin D, and fluoride Panel report 1998; Trace elements, vitamin A, and vitamin K Panel report, 2001).

Nutrient	Indicators evaluated	Indicators used for EAR/RDA assessment
Vitamin A	Dark adaptation	Under controlled feeding conditions, dark adaptation is one of the most sensitive indicators of a change in vitamin A deficiency; however, in addition zinc deficiency and severe protein deficiency may affect dark adaptation response; dark adaptation could be used to estimate the EAR but without assurance of adequate tissue levels to meet non-visual needs
	Pupillary response test (threshold of light at which a pupillary response first occurs under dark adapted conditions)	No data available relating pupillary threshold sensitivity as determined by this test to usual vitamin A intake
	Plasma retinol concentration	Plasma retinol concentration is under tight homeostatic control and insensitive to liver vitamin A stores and is neither related to levels of usual vitamin A intake (preformed vitamin A or provitamin A carotenoids); due to its insensitivity it was not chosen as indicator for a population for estimating an EAR for vitamin A
	Total liver reserves measured by isotope dilution technique	Not used since no studies have been conducted in which detailed and long-term dietary data have been obtained to correlate it with liver reserves of vitamin A determined by an isotope dilution technique

Nutrient	Indicators evaluated	Indicators used for EAR/RDA assessment
Vitamin A	Relative dose response (RDR)	RDR would allow indirect assessment of relative adequacy of hepatic vitamin A stores; not used since little data are available relating usual dietary intake of populations to RDR test values
	Conjunctival impression cytology (CIC) tests	Not used as a functional indicator for the EAR of vitamin A, since only few data are available relating CIC status to dietary vitamin A intake
	Immune function tests	These tests are affected by many other factors and therefore immune function tests could not be used as an indicator for the EAR of vitamin A
	Maintenance of adequate body vitamin A stores	<p>Calculated on the basis of the amount of dietary vitamin A required to maintain a given body pool size of vitamin A in well nourished subjects according to the formula $A \times B \times C \times D \times E \times F$ with</p> <p>A = % of body vitamin A stores lost /day when ingesting a vitamin A-free diet (0.5 %)</p> <p>B = minimum acceptable liver vitamin A reserves (20 µg/g)</p> <p>C = the liver weight : body weight ratio (1:33)</p> <p>D = reference weight for a specific age group (adult women and men 61 and 76 kg, respectively)</p> <p>E = ratio of total body to liver vitamin A reserves (10:9)</p> <p>F = efficiency of storage of ingested vitamin A (approximately 40%)</p>

Nutrient	Indicators evaluated	Indicators used for EAR/RDA assessment
Vitamin D	Serum 25(OH)D concentration	Considered as the best indicator for the determination of adequacy of vitamin D intake, since it reflects total cutaneous production and dietary ingestion
	Serum PTH concentration in conjunction with 25(OH)D	PTH is inversely related to serum 25(OH)D concentration and together they are considered a valuable indicator for vitamin D status
	Serum vitamin D and 1,25(OH) ₂ D concentrations	Considered to be not a good indicator due to short half-life, dependence on recent ingestion and sunlight exposure, and due to tight regulation by a variety of factors such as serum calcium, PTH, and other hormones
	Maintenance of a healthy skeleton	In neonates and children bone development and prevention of rickets are good indicators for vitamin D status; for adults bone mineral content, loss of bone mineral density (BMD), and fracture risk in combination with serum 25(OH)D and PTH concentrations are most valuable indicators for vitamin D status

Nutrient	Indicators evaluated	Indicators used for EAR/RDA assessment
Vitamin K	Prothrombin time (PT)	The classical PT is not a sensitive indicator for vitamin K status and does not respond to a change in dietary vitamin K intake in healthy subjects
	Plasma factor VII activity	Factor VII is not a sensitive indicator for vitamin K status and does usually not respond to changes in vitamin K intake in healthy individuals
	Plasma and serum phylloquinone concentrations	These indicators have been shown to reflect recent dietary vitamin K intakes, but strength of its association has been varied according to differences in intake assessment methodology
	Urinary γ -carboxy glutamyl residues (urinary GLA excretion), plasma under-carboxylated prothrombin (PIVKA-II), and plasma under- γ -carboxylated osteocalcin (ucOC)	These recently developed indicators sensitive to vitamin K intake were not used for establishing an EAR because of uncertainties surrounding their true physiological significance and the lack of sufficient dose-response data from intervention studies with graded intakes of vitamin K

4. Dietary Reference Intakes (EAR, RDA, AI) for various age groups for Vitamins A, D, and K

Table II: DRI values for vitamins A, D, and K for **Infants (0-6 months)** (Calcium, phosphorus, magnesium, vitamin D, and fluoride Panel report, 1998; Trace elements, vitamin A, and vitamin K Panel report, 2001).

Nutrient	EAR	RDA	AI
Vitamin A	-	-	400 µg/day
Vitamin D*	-	-	5 µg (200 IU)/day
Vitamin K ⁺	-	-	2 µg/day

- * serum 25(OH)D concentration below 27.5 nmol/L is being used as key indicator for vitamin D deficiency in infants, neonates, and young children
- + based on a reported average intake of vitamin K from human milk of 0.78 L/day and the average phyloquinone milk concentration of 2.5 µg/day

Table III: DRI values for vitamins A, D, and K for **Infants (7-12 months)** (Calcium, phosphorus, magnesium, vitamin D, and fluoride Panel report, 1998; Trace elements, vitamin A, and vitamin K Panel report, 2001).

Nutrient	EAR	RDA	AI
Vitamin A	-	-	500 µg/day
Vitamin D*	-	-	5 µg (200 IU)/day
Vitamin K ⁺	-	-	2.5 µg/day

- * serum 25(OH)D concentration below 27.5 nmol/L is being used as key indicator for vitamin D deficiency in infants, neonates, and young children
- + extrapolated from the AI for infants (0-6 months)

Table IV: DRI values for vitamins A, D, and K for **Children (1-3 years)** (Calcium, phosphorus, magnesium, vitamin D, and fluoride Panel report, 1998; Trace elements, vitamin A, and vitamin K Panel report, 2001).

Nutrient	EAR	RDA	AI
Vitamin A	210 µg/day	300 µg/day ^o	-
Vitamin D*	-	-	5 µg (200 IU)/day
Vitamin K ⁺	-	-	30 µg/day

- ^o a coefficient of variation CV of 20 % is being used calculated from turnover studies in man
- * serum 25(OH)D concentration below 27.5 nmol/L is being used as key indicator for vitamin D deficiency in infants, neonates, and young children
- + set on the basis of median intake for adult males and females reported by the NHANES III survey; extrapolated according to body weight

Table V: DRI values for vitamins A, D, and K for **Children (4-8 years)** (Calcium, phosphorus, magnesium, vitamin D, and fluoride Panel report, 1998; Trace elements, vitamin A, and vitamin K Panel report, 2001).

Nutrient	EAR	RDA	AI
Vitamin A	275 µg/day	400 µg/day ^o	-
Vitamin D*	-	-	5 µg (200 IU)/day
Vitamin K ⁺	-	-	55 µg/day

- ^o a coefficient of variation CV of 20 % is being used calculated from turnover studies in man
- * serum 25(OH)D concentration below 27.5 nmol/L is being used as key indicator for vitamin D deficiency in infants, neonates, and young children
- + set on the basis of median intake for adult males and females reported by the NHANES III survey; extrapolated according to body weight

Table VI: DRI values for vitamins A, D, and K for **Children (9-13 years)** (Calcium, phosphorus, magnesium, vitamin D, and fluoride Panel report, 1998; Trace elements, vitamin A, and vitamin K Panel report, 2001).

Nutrient	EAR	RDA	AI
Vitamin A	445/420 µg/day ^o	600/600 µg/day ^{o*}	-
Vitamin D ^{**}	-	-	5 µg (200 IU)/day
Vitamin K ⁺	-	-	60 µg/day

- * a coefficient of variation CV of 20 % is being used calculated from turnover studies in man;
- ^o male/female
- ** serum 25(OH)D concentration below 27.5 nmol/L is being used as key indicator for vitamin D deficiency in infants, neonates, and young children
- + set on the basis of median intake for adult males and females reported by the NHANES III survey; extrapolated according to body

Table VII: DRI values for vitamins A, D, and K for **Adolescents (14-18 years)** (Calcium, phosphorus, magnesium, vitamin D, and fluoride Panel report, 1998; Trace elements, vitamin A, and vitamin K Panel report, 2001).

Nutrient	EAR	RDA	AI
Vitamin A	630/485 µg/day ^o	900/700 µg/day ^{o*}	-
Vitamin D ^{**}	-	-	5 µg (200 IU)/day
Vitamin K ⁺	-	-	75 µg/day

- * a coefficient of variation CV of 20 % is being used calculated from turnover studies in man;
- ^o male/female;
- ** serum 25(OH)D concentration below 27.5 nmol/L is being used as key indicator for vitamin D deficiency in infants, neonates, and young children
- + set on the basis of median intake for adult males and females reported by the NHANES III survey; extrapolated according to body weight

Table VIII: DRI values for vitamins A, D, and K for **Adults (19-50 years)** (Calcium, phosphorus, magnesium, vitamin D, and fluoride Panel report, 1998; Trace elements, vitamin A, and vitamin K Panel report, 2001).

Nutrient	EAR	RDA	AI
Vitamin A ⁺	625/500 µg/day ^o	900/700 µg/day ^{o*}	-
Vitamin D ^{**}	-	-	5 µg (200 IU)/day
Vitamin K ⁺	-	-	120/90 µg/day ^o

- + EAR of preformed vitamin A required to assure an adequate body vitamin A reserve in an adult male would be $0.005 \times 20 \mu\text{g/g} \times 0.03 \times 76 \text{ kg} \times 1.1 \times 2.5 = 627 \mu\text{g/day}$; with the reference weight of 61 kg for women, the EAR would be 503 µg/day
- * a coefficient of variation CV of 20 % is being used calculated from turnover studies in man
- ^o male/female
- ** The AI for vitamin D is determined on the basis of an intake maintaining a serum 25(OH)D concentration > 30 nmol/L regardless of exposure to sunlight, since there is little scientific data which relates vitamin D intake, bone health, and vitamin D status as determined by serum 25(OH)D and PTH concentrations in this age group
- + The AI for adults for vitamin K is based on reported median dietary intake data from NHANES III by healthy population groups and the highest intake value reported for the four adult groups was used

Table IX: DRI values for vitamins A, D, and K for **Adults (51 and older)** (Calcium, phosphorus, magnesium, vitamin D, and fluoride Panel report, 1998; Trace elements, vitamin A, and vitamin K Panel report, 2001).

Nutrient	EAR	RDA	AI
Vitamin A	625/500 µg/day ^o	900/700 µg/day ^{o*}	-
Vitamin D ^{**}	-	-	10 µg (400 IU)/day ⁺
Vitamin K ^{&}	-	-	120/90 µg/day ^o

* a coefficient of variation CV of 20 % is being used calculated from turnover studies in man

** The AI for vitamin D is based on bone loss as an indicator for adequacy and the observation that cutaneous production of vitamin D is decreased with aging

^o male/female

⁺ Evidence is strong that elderly (> 70 years) are at high risk of hypovitaminosis D, and increasing osteoporosis with increased risk for skeletal fractures. A AI of 15 µg (600 IU)/day was set for adults over 70 years, independent of exposure to sunlight and stores.

[&] The AI for adults for vitamin K is based on reported median dietary intake data from NHANES III by healthy population groups and the highest intake value reported for the four adult groups was used



Vitamin A activity of provitamin A carotenoids: There are a number of sources for dietary vitamin A. Preformed vitamin A is abundant in animal derived foods, whereas provitamin A carotenoids (alpha-carotene, beta-carotene, beta-cryptoxanthin) are present in dark leafy vegetables and fruits. Carotene bioavailability and bioconversion to vitamin A are affected by a number of factors. Bioavailability can be affected by different processing methods of the same food and whether it is dissolved in oil or associated with plant matrix materials. Absorbed beta-carotene is converted by the enzyme beta-carotene-15,15'-dioxygenase within the intestinal absorptive cells. The carotene : retinol equivalency ratio ($\mu\text{g} : \mu\text{g}$) of a low dose (up to 2 mg) of purified beta-carotene in oil is about 2:1 (2 μg of beta-carotene in oil yields 1 μg of retinol). This ratio is derived from the determination of the activity required to correct abnormal dark adaptation in vitamin A-deficient individuals and from studies using the stable isotope reference method.

Retinol activity equivalents (RAE) for various dietary provitamin A carotenoids have been set based on studies comparing the efficiency of absorption of beta-carotene after feeding physiological amounts of beta-carotene in oil, in individual foods, and as part of a mixed vegetable and fruit diet. Recent results indicate that approximately 6 μg of beta-carotene from a mixed diet is nutritionally equivalent to 1 μg of beta-carotene in oil, and therefore the retinol activity equivalent (RAE) ratio for beta-carotene from food is estimated to be (6 x 2:1) or 12:1. Ratios of RAE for alpha-carotene and cryptoxanthin were set at 24:1. This increase in conversion ratio compared to the

former ratio (6:1 for dietary beta-carotene) means that a larger amount of carotene-rich fruits and vegetables is needed to be consumed to meet the vitamin A requirement. Expressed in International Units (IU) vitamin A activity = 0.3 μg of all-trans-retinol = 3.6 μg of all-trans-beta-carotene = 7.2 μg of other provitamin A carotenoids (Table X).

Table X: Absorption and bioconversion of ingested provitamin A carotenoids to retinol based on the new retinol activity equivalent (RAE) ratio (according to Trace elements, vitamin A, and vitamin K Panel report, 2001)

Consumed as	Absorbed as	Bioconverted to
Dietary or supplemental vitamin A (1 μg)	Retinol	Retinol (1 μg)
Supplemental purified beta-carotene (2 μg)	Beta-carotene	Retinol (1 μg)
Dietary beta-carotene (12 μg)	Beta-carotene	Retinol (1 μg)
Dietary alpha-carotene or beta-cryptoxanthin (24 μg)	Alpha-carotene or beta-cryptoxanthin	Retinol (1 μg)

5. Criteria used for the establishment of Tolerable Upper Levels of Intake (UL)

A nutrient can produce more than one adverse health effect (or end point) and the no-observed-adverse-effect (NOAEL) and lowest-observed-adverse-effect (LOAEL) levels for these different effects will be different. The Committee decided to use that critical endpoint (adverse effect) with the lowest NOAEL (or LOAEL). The use of the most sensitive endpoint for the derivation of the Tolerable Upper Level of Intake (UL) (using a single uncertainty factor UF) will ensure protection against all other adverse health effects which may occur with higher overall chronic intakes.

For infants case reports of hypervitaminosis A were used to identify a lowest observed adverse effect level (LOAEL) with bulging fontanel as parameter from which a UL was derived. For infants a UL could not be determined for vitamins D and K because of lack of data or of adverse effects in this particular age group. When possible ULs for infants and children were determined by extrapolation from the UL for adults based on body weight differences or were based on human milk intake in exclusively breast-fed infants.

Table XI: Parameters (adverse health effects) used or considered for the identification of NOAEL/LOAEL as basis for the derivation of Tolerable Upper Levels of Intake (UL) for vitamins A, D, and K in adults.

Nutrient	Criteria for NOAEL	Criteria for LOAEL	Comments
Vitamin A	No data were available to derive a NOAEL in infants	Bulging fontanel was identified in infants as basis for a LOAEL	There are only 4 case reports after doses of 5500 to 6750 µg/day of vitamin A over 1–3 months; other side effects were anorexia, hyperirritability, occipital edema, increased intracranial pressure, and skin lesions and desquamation; there were limited data in children and adolescents and the UL was extrapolated from those for adults
	Teratogenicity was selected as the critical adverse effect to base an UL for women in the reproductive age	Liver abnormalities (hepatotoxicity) were chosen for all other adults and other than women in the reproductive age; data must show grossly elevated hepatic vitamin A levels or hypertrophy of Ito cells (no alcoholism, no concomitant liver hepatitis, and no use of hepatotoxic drugs)	Study findings on reduced bone mineral density and increased risk of hip fracture were not considered useful for setting a UL for vitamin A because of the conflicting findings and the lack of other studies confirming these data

Table XI: Parameters (adverse health effects) used or considered for the identification of NOAEL/LOAEL as basis for the derivation of Tolerable Upper Levels of Intake (UL) for vitamins A, D, and K in adults.

Nutrient	Criteria for NOAEL	Criteria for LOAEL	Comments
Vitamin D	Relation between vitamin D intake at 60 µg (2400 IU)/day and significant increase in serum calcium concentrations although in normal range	Hypercalcemia defined as serum calcium concentrations above 2.75 mmol/L	Available animal data were not used to derive a UL for adults, because these data were judged to have greater associated uncertainty than human data
Vitamin K	None	None	Since no adverse effects have been associated with vitamin K consumption either in humans or animals from food or supplements, a quantitative risk assessment cannot be performed and there are no criteria for the determination of a NOAEL or LOAEL. In laboratory animals, no adverse effects were reported with administration of up to 25 g/kg of phylloquinone either parenterally or orally

Table XII: No-observed-adverse-effect (NOAEL) and lowest-observed-adverse-effect (LOAEL) intake levels, and uncertainty factors (UF) used for determination of Tolerable Upper Levels of Intake (UL) for vitamins A, D, and K in adults.

Nutrient	NOAEL	UF ₁	LOAEL	UF ₂	UL for Adults
Vitamin A	4500 µg/day ⁺	1.5	14000 µg/day ⁺⁺	5	3000 µg/day
Vitamin D	60 µg (2400 IU)/day	1.2	95 µg (3800 IU)/day	-	50 µg (2000 IU)/day
Vitamin K	None	-	None	-	None

Comments to Table XII:

Vitamin A (preformed)

⁺ NOAEL based on human epidemiological studies evaluating toxicity of vitamin A intake (food and supplements) shortly before or during pregnancy; there are limited data to clearly define a dose-response relationship; evidence of no adverse effect at or below intakes of 4500 µg/day was considered sufficient to define this level as the NOAEL for women of the reproductive age. Since there are substantial data showing no adverse effects at doses up to 3000 µg/day of vitamin A supplements a UF higher than 1.5 was considered not justified. The UL for adolescent girls was adjusted on the basis of relative body weight.

⁺⁺ For all other adults (excluding women of the reproductive age) liver abnormalities were used as criteria to derive a LOAEL at 14000 µg/day. Due to the irreversibility of these adverse effects and the extrapolation from a LOAEL, a UF of 5 was selected and a UL of 3000 µg/day for adults other than women of the reproductive age was obtained. Case reports of hypervitaminosis A in infants using bulging fontanel as parameter were used to identify a LOAEL for infants (6000 µg/day) and to derive at a UL for infants (600 µg/day; UF=10). A NOAEL for infants could not be assessed due to lack of data. The UL for children and adolescents were extrapolated from the UL established for adults on the basis of relative body weight.

The UL is based on healthy populations in developed countries. In fortification and supplementation programs for the prevention and treatment of vitamin A deficiency in developing countries doses exceeding the current UL for vitamin A are being used, but the UL is not meant to apply to communities of malnourished individuals receiving vitamin A to prevent vitamin A deficiency.

Provitamin A: high beta-carotene (provitamin A) intake has not been shown to cause hypervitaminosis A

Vitamin D

UL is based on NOAEL; the LOAEL was not used for the derivation of UL; UL of 50 µg (2000 IU)/day also valid for children aged 1 year and older, and for pregnant or lactating women; for children aged < 1 year the UL is set to 25 µg (1000 IU)/day based on hypercalcemia and findings on linear growth

Vitamin K

The data on adverse effects from high dose vitamin K intakes are not sufficient for a quantitative risk assessment, and therefore an UL cannot be derived. No adverse effects have been reported with consumption of vitamin K with food or supplements.

6. Values for No-Observed-Adverse-Effect (NOAEL), Lowest-Observed-Adverse-Effect (LOAEL) levels, and Tolerable Upper Levels of Intake (UL) for Vitamins A, D, and K for adults

Table XIII: NOAEL, LOAEL, and UL for vitamins A, D, and K for adults (19-50 years)

Nutrient	NOAEL	LOAEL	UL
Vitamin A	4500 µg/day	14000 µg/day	3000 µg/day
Vitamin D*	60 µg (2400 IU)/day	95 µg (3800 IU)/day	50 µg (2000 IU)/day
Vitamin K	None	None	None

* For comments see Table XII



7. Reported dietary and supplement intakes of Vitamins A, D, and K (USA data)

Table XIV: Dietary and supplement intake of vitamins A, D, and K for adults in the USA

Nutrient	Dietary Intake		Supplement Intake	
	Men	Women	Men	Women
Vitamin A	1965 µg/day ⁺⁺	1050 µg/day ^{oo}	1500 – 3000 µg/day [§]	
Vitamin D ^{**}	No data given	2.9 µg [*] (114 IU)/day	20 µg ⁺ (800 IU)/day	17.2 µg ⁺ (686 IU)/day
Vitamin K	340 µg/day [*]		367 µg/day ^o	

- * median intake data from 2nd National Health and Nutrition Examination Survey (NHANES II); + ninety-fifth percentile
- ** persons adhering to a diet high in fish and consuming large amounts of fortified (9.6 µg (385 IU)/L) milk may have a higher intake of vitamin D; for most people vitamin D intake from food and supplements is unlikely to exceed the UL. Persons who are at the upper end of the range for both supplements and with high intakes of fish and fortified milk may be at risk for vitamin D toxicity
- o highest intake from food and supplements
- ++ highest reported intake at the ninety-fifth percentile in males 31 through 50 years
- oo highest median intake for any gender and life stage group was consumed by lactating women
- § intakes at the ninety-fifth percentile for adult Americans taking supplements; less than 5% of pregnant women had dietary and supplement intakes exceeding the UL

8. Results from the Panel on Calcium, Phosphorus, Magnesium, **Vitamin D**, and Fluoride, and from the Panel on Trace Elements, **Vitamin A**, and **Vitamin K**

The overall recommendations can be summarized as follows:

Vitamin A

- Requirement for adults have been slightly reduced to 900/700 µg/day. The EAR/RDA is expressed as µg retinol/day and the formerly used retinol equivalent is abandoned.
- The EAR is based on that daily intake which is required to maintain a given body pool size in a well nourished group of subjects. Based on the liver half-life of vitamin A a coefficient of variation of 20 percent is used for calculating the RDA.
- Insufficient data are available to set an EAR for infants. A AI was extrapolated from intakes from human milk.
- The EAR for children and adolescents is extrapolated from adult data by using the metabolic body weight.
- Retinol activity equivalents (RAE) were introduced covering absorption and bioconversion of dietary provitamin A carotenoids into retinol. The retinol activity equivalent (RAE) ratio for dietary beta-carotene from food is estimated to be (6x2:1) or 12:1. This increase in conversion ratio compared to the former ratio of 6:1 for dietary beta-carotene to yield 1 µg retinol means that a larger amount of carotene-rich fruits and vegetables is needed to be consumed to meet the vitamin A requirement. The existing recommendations for increased consumption of carotenoid-rich fruits and vegetables (five servings per day; approximately 5-6 mg/day of provitamin A carotenoids) for their health-promoting benefits are strongly supported.
- A tolerable upper level of intake of 3000 µg/day (10000 IU) was set for women in the reproductive age using teratogenicity as the critical adverse effect. Evidence of no adverse effect at or below 4500 µg/day was considered sufficient to define this level as the NOAEL and an uncertainty factor UF of 1.5 was considered adequate. The UL for adolescent girls was adjusted on the basis of body weight.

- For all other adults (excluding women of the reproductive age) liver abnormalities were used as criteria to derive a LOAEL at 14000 µg/day. A UF of 5 was selected to derive at a UL of 3000 µg/day.
- Case reports of hypervitaminosis A in infants were used to identify a LOAEL for infants (6000 µg/day) with bulging fontanel as parameter and to derive a UL for infants of 600 µg/day (UF = 10).
- Study findings on reduced bone mineral density and increased risk of hip fracture were not considered as basis for a UL for vitamin A, because of conflicting results and lack of other studies confirming these data.
- High intakes of provitamin A carotenoids will not lead to hypervitaminosis A.

Vitamin D

- No EAR value for either age group and gender could be determined, since most of the studies were affected by factors influencing the cutaneous sunlight mediated synthesis of vitamin D (skin pigmentation, season of the year, amount of body surface covered, use of sunscreen etc). In addition there are limitations to the vitamin D content of various foods. Therefore only AI were set.
- Serum 25(OH)D is considered as the best indicator for the determination of adequacy of vitamin D intake, since it reflects total cutaneous production and dietary ingestion.
- Little information is available about the concentration that is essential to maintain normal calcium metabolism and peak bone mass in older children and in young and middle-aged adults.
- In neonates and children bone development and prevention of rickets are good indicators for vitamin D status. The vitamin D intake of formula-fed infants not exposed to sunlight should be at least 5 µg (200 IU)/day.
- Aging significantly decreases the capacity of human skin to produce vitamin D. Using bone loss as an indicator of adequacy and data from

studies in women between ages 51 through 70 years, for this age group a AI of 10 µg (400 IU)/day was set.

- Evidence is strong that elderly (> 70 years) are at high risk of hypovitaminosis D and increasing osteoporosis with increased risk for skeletal fractures. A AI of 15 µg (600 IU)/day was set for adults over 70 years, independent of exposure to sunlight and vitamin D stores.
- Hypercalcemia defined as serum calcium concentrations above 2.75 mmol/L was observed at a dose of 95 µg (3800 IU)/day (LOAEL). Intakes of 60 µg (2400 IU)/day caused a significant rise in serum calcium concentration, but it remained within the normal range, and this was determined as the NOAEL on which the UL of 50 µg (2000 IU)/day was based using an uncertainty factor UF of 1.2.
- For children and adolescents a UL for vitamin D could not be determined because of lack of data suitable to derive a NOAEL or LOAEL. Available limited data suggest that the UL for adults is also appropriate for these age groups.
- Available data indicate that excessive vitamin D intake is to be considered as probable risk factor for hypercalcemia in sensitive infants aged below one year. Based on a NOAEL of 45 µg (1800 IU)/day and a UF of 1.8 the UL for infants up to 1 year was set at 25 µg (1000 IU)/day.
- For most subjects vitamin D intake from food and cautious supplement use is unlikely to exceed the UL.

Vitamin K

- Because of lack of data to derive an EAR an adequate intake AI is set based on representative dietary intake data resulting from the Third National Health and Examination Survey (NHANES III) in healthy adult individuals.

- Adequate intakes for infants were based on a reported average intake of vitamin K from human milk of 0.78 L/day and the known average phyloquinone milk concentration of 2.5 µg/day.
- Likewise, adequate intakes for children and adolescents were based on intake data from NHANES III for adults extrapolated according to body weight.
- The recently developed indicators sensitive to vitamin K intake (urinary γ-carboxyglutamyl residues (urinary GLA excretion), plasma under-γ-carboxylated prothrombin (PIVKA-II), and plasma under-γ-carboxylated osteocalcin (ucOC) were not used for establishing an EAR due to uncertainties with regard to their physiological significance and the lack of sufficient dose-response data from intervention studies with graded intakes of vitamin K.
- A role of vitamin K in bone health has been discussed, but available evidence at this time was considered to be insufficient to determine a potential in risk reduction of osteoporosis.
- A UL for vitamin K could not be set for all age groups, since data on adverse effects from high dose vitamin K intakes are not sufficient for a quantitative risk assessment. However, no adverse effects have been reported with consumption of vitamin K with food or supplements or with high intakes in animal studies.

9. Recommendation for Future Research by the Panel on Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride, and by the Panel on Trace Elements, Vitamin A, and Vitamin K

The FNB Panels have identified gaps in scientific data which would allow to have the overall recommendations for DRIs supported by a broader scientific basis. These recommendations are summarized below:

Vitamin A

- Effects of food matrices (eg, carotenoids in milk and supplements) on the bioavailability of provitamin A carotenoids
- Age-related differences in the bioavailability of vitamin A
- Definition of critical endpoints for the population assessment for vitamin A and evaluation of their association with liver vitamin A stores
- Effect of dietary vitamin A and vitamin A status on turnover and utilization of vitamin A in man
- Relationship of bioactive vitamin A indicators (eg, retinoic acid) to dietary vitamin A intake
- Effects of pregnancy and lactation on maternal vitamin A turnover
- Effect of the interaction of vitamin A with other nutrients, and of food processing on the bioavailability of vitamin A

Vitamin D

- Evaluation of different intakes of vitamin D throughout lifespan and the influence of sunscreens
- In adolescents research is needed on the effect of various intakes of vitamin D on circulating concentrations of 25(OH)D and 1, 25(OH)₂D during winter and limited exposure to sunlight. Similarly, in healthy young adults more studies are needed that evaluate various doses of vitamin D in the absence of sunlight exposure, in order to determine better the requirement in this age group
- Evaluation of other parameters of calcium metabolism as they relate to vitamin D status including circulating concentrations of PTH

- Development of methodologies to assess changes in body stores of vitamin D in absence of sunlight exposure to be used for all life stage groups.

Vitamin K

- Clinical studies of vitamin K supplementation to elucidate the physiological significance of under- γ -carboxylated osteocalcin (ucOC); relation of this indicator to overall bone health and bone integrity
- Research on the function of vitamin K-dependent proteins and their role in human physiology
- Knowledge on a possible role of vitamin K in promoting human health other than that mediated by the known Gla-containing vitamin K-dependent proteins
- Studies on the bioavailability of dietary vitamin K

10. References

- 1 Dietary Reference Intakes for Calcium, phosphorus, magnesium, vitamin D and fluoride. A report by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride; Food and Nutrition Board, Institute of Medicine, National Academy Press, Washington, D.C., 1998 (<http://www.nap.edu>)
- 2 Dietary Reference Intakes for Trace Elements, Vitamins A and K. A report by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Trace Elements, Vitamins A and K; Food and Nutrition Board, Institute of Medicine, National Academy Press, Washington, D.C., 2001 (<http://www.nap.edu>)
- 3 Dietary Reference Intakes: «Application in Dietary Assessment». A Report of the Subcommittee on Interpretation and Uses of Dietary Reference Intakes and Upper Reference Levels of Nutrients, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes; Food and Nutrition Board, Institute of Medicine, National Academy Press, Washington, D.C., 2001 (<http://www.nap.edu>)





Vitamins

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