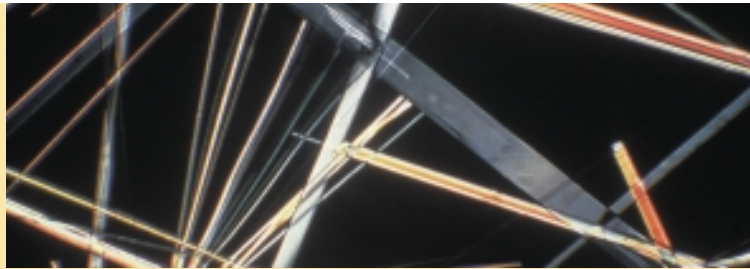


Dietary Antioxidants

Dietary Reference Intakes DRI (US Food and Nutrition Board)



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A Summary of the Panel Report

This report has been elaborated by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Vitamin C, Vitamin E, and Selenium, and on β -carotene and other carotenoids (α -carotene, β -cryptoxanthin, lutein, lycopene, and zeaxanthin) and the Subcommittee on Upper Reference Levels of Nutrients, US Food Nutrition Board (FNB) with active involvement of Health Canada (1). It established a set of science-based reference values for these dietary antioxidants to replace the previously published Recommended Dietary Allowances (RDAs) for the USA and the Recommended Nutrient Intakes (RNIs) for Canada.

This summary covers vitamins C and E, β -carotene and other carotenoids and is based on the respective US FNB Panel report.

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 Allowances 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 an RDA cannot be calculated, an *Adequate Intake AI* is set instead of an 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 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.

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

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)

DRIs and Intake

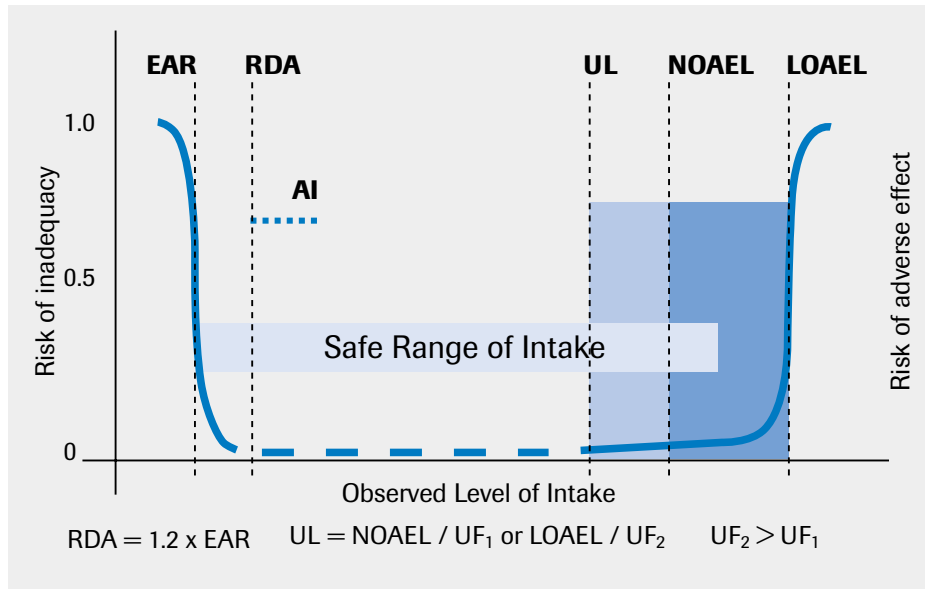


Fig.1: Dietary Reference Intakes (EAR; RDA; AI; UL), no-observed-adverse-effect (NOAEL), and lowest-observed-adverse-effect (LOAEL) intake levels. The Estimated Average Requirement (EAR) is the intake at which the risk of inadequacy is 0.5 (50%) to an individual. The Recommended Dietary Allowance (RDA) 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 assessing the diets of 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 as a pre-publication and is dealing with «Application of Dietary Reference Intakes in Dietary Assessment» (2). 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.

Use of DRIs for Planning of Diets

For the Individual

RDA: aim for that 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 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 Value DRV) which will be determined by the regulatory bodies, in the USA by the FDA. There is at present no indication by the US FDA on an approximate timeframe.

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 ingestion)
- 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 the dietary antioxidants (vitamins C and E, β -carotene and the carotenoids) (Table I):

Table I: Dietary Antioxidants: Indicators evaluated and actually used for the assessment of Estimated Average Requirements (EAR)

Nutrient	Indicators evaluated	Indicators used for EAR/RDA assessment
Vitamin C	LDL oxidation; biomarkers of lipid peroxidation; vascular function; antioxidant function in leukocytes; protection against inflammatory oxidative stress; cellular markers of DNA damage; urinary markers of DNA damage; parameters of immune response and common cold; collagen-related measures as a functional indicator; carnitin status; relationship between vitamin C intake and periodontal health, and other chronic diseases (cancer, cardiovascular disease), eye disease (cataract); cognitive function and memory	Vitamin C intake maintaining near-maximal neutrophil concentration with minimal urinary loss
Vitamin E	Markers of lipid peroxidation (TBARS, malondialdehyde, conjugated dienes, pentane, ethane, F ₂ -isoprostanes; DNA oxidation products; urinary metabolites (2,5,7,8-tetramethyl-2-(2'-carboxy-ethyl)-6-hydroxychroman); vitamin E kinetics, metabolism, pool size determination; plasma vitamin E concentration; parameters of immune response; hydrogen peroxide-induced erythrocyte hemolysis; relationship between vitamin E intake and chronic diseases (cardiovascular disease, cancer, diabetes mellitus, central nervous system disorders), eye disease (cataract); relationship between dietary high PUFA intake and vitamin E intake; (RRR)- α -tocopherol plasma concentration	Relationship between plasma (RRR)- α -tocopherol concentration and hydrogen peroxide-induced in vitro erythrocyte hemolysis; plasma (RRR)- α -tocopherol concentration of 12 μ mol/L was chosen associated with normal in vitro hemolysis

Table I: Dietary Antioxidants: Indicators evaluated and actually used for the assessment of Estimated Average Requirements (EAR)

Nutrient	Indicators evaluated	Indicators used for EAR/RDA assessment
β-Carotene and other carotenoids	Vitamin A equivalency	Will be considered in concert with the evaluation of DRIs for vitamin A
	Markers of antioxidant activity for β-carotene from food and from supplements (DNA strand breaks, lowered copper-induced oxidation of low density lipoproteins; lipid peroxidation; breath pentane)	Data are inconsistent and considered inadequate for the estimation of a requirement for β-carotene; there are no convincing data that β-carotene is an in vivo antioxidant
	Gap junctional communication	More research required to ascertain whether carotenoids influence gap junction communication processes in vivo
	Parameters of immune function	It is not confirmed whether the observed effects are specific for carotenoids and usefulness of these parameters has to be established
	Relationship of carotenoid intake and plasma and tissue concentration to chronic disease (mortality; cancer/cardiovascular disease: epidemiological and intervention studies; age-related macular disease; cataract)	Plasma and tissue concentrations of carotenoids have been associated with a variety of health outcomes: higher concentrations are associated with lower risk of cancer, coronary heart disease, and all-cause mortality could be used as indicators for requirement, but it is unclear whether the observed health benefit is due to carotenoids per se or other substances in carotenoid-rich food. The data are considered suggestive of prudent intake levels, but not for the determination of requirement. Human studies using dietary interventions with carotenoid-rich foods in varying population groups suggest that 3-6 mg/day of β-carotene from food source is prudent to maintain plasma β-carotene concentrations associated with a lower risk of various chronic disease outcome

4. Dietary Reference Intakes (EAR, RDA, AI) for various age groups for Dietary Antioxidants

Table II: DRI values for *Infants (0-6 months)*
(Dietary Antioxidants panel report 2000).

Nutrient	EAR	RDA	AI
Vitamin C*	-	-	40 mg/day
Vitamin E*	-	-	4 mg/day
β-Carotene and other carotenoids	-	-	none

* this recommendation is based on the mean volume of human milk intake of 0.78 L/day and an average concentration of vitamin C in human milk of 50 mg/L and of vitamin E of 4.9 mg/L

Table III: DRI values for *Infants (7-12 months)*
(Dietary Antioxidants panel report 2000).

Nutrient	EAR	RDA	AI
Vitamin C*	-	-	50 mg/day
Vitamin E*	-	-	5 mg/day
β-Carotene and other carotenoids	-	-	none

* this recommendation is based on the mean volume of human milk intake of 0.60 L/day and an average concentration of vitamin C in human milk of 45 mg/L and an average vitamin C intake of 22 mg/day from solid foods for formula-fed infants.
Vitamin E requirement is estimated by extrapolation from the AI of infants 0-6 months.

Table IV: DRI values for *Children (1-3 years)*
(Dietary Antioxidants panel report 2000).

Nutrient	EAR	RDA	AI
Vitamin C*	13 mg	15 mg	-
Vitamin E*+	5 mg	6 mg	-
β-Carotene and other carotenoids**	none	none	none

* no data are available to base on an EAR for children 1 through 18 years of age; EARs for children and adolescents were estimated from adult values based on lean body mass and need for growth; recommended intakes for infants (> 1 year) are based on an Adequate Intake (AI) reflecting the observed mean vitamin intake of infants fed principally with human milk

+ DRIs for α-tocopherol include (RRR)-α-tocopherol and the other 2R-stereoisomers (RSR-, RRS-, and RSS-α-tocopherol) and do not include amounts obtained from the other seven naturally occurring forms (β, γ, δ-tocopherols and the tocotrienols). The biopotency of synthetic vitamin E (all-rac-α-tocopherol) is considered as half of that of the natural vitamin E on the weight basis, i.e. 15 mg of the natural vitamin E is equivalent to 30 mg of the synthetic all-rac-α-tocopherol

** the only clear function of certain carotenoids that is firmly linked to a health outcome is the pro-vitamin A activity of some dietary carotenoids (α-carotene, β-carotene, and β-cryptoxanthin) and their role in the prevention of vitamin A deficiency. A requirement for carotenoids based upon their vitamin A activity will be done in conjunction with the evaluation of the DRIs for vitamin A which will be addressed in a subsequent DRI report.

All other indicators evaluated to determine a requirement for β-carotene and other carotenoids were considered insufficient and require more research, but existing recommendations for increased consumption of carotenoid-rich fruits and vegetables are supported.



Table V: DRI values for **Children (4-8 years)**
(Dietary Antioxidants panel report 2000).

Nutrient	EAR	RDA	AI
Vitamin C*	22 mg	25 mg	-
Vitamin E**	6 mg	7 mg	-
β-Carotene and other carotenoids**	none	none	none

* + and**: For these footnotes refer to Table IV

Table VII: DRI values for **Adolescents (14-18 years)**
(Dietary Antioxidants panel report 2000).

Nutrient	EAR	RDA	AI
Vitamin C*	63/56 mg ^o	75/65 mg ^o	-
Vitamin E**	12 mg	15 mg	-
β-Carotene and other carotenoids**	none	none	none

* + and**: For these footnotes refer to Table IV

^o males/females

Table VI: DRI values for **Children (9-13 years)**
(Dietary Antioxidants panel report 2000).

Nutrient	EAR	RDA	AI
Vitamin C*	39 mg	45 mg	-
Vitamin E**	9 mg	11 mg	-
β-Carotene and other carotenoids**	none	none	none

* + and**: For these footnotes refer to Table IV

Table VIII: DRI values for **Adults (19-50 years)**
(Dietary Antioxidants panel report 2000).

Nutrient	EAR	RDA	AI
Vitamin C*	75/60 mg ^o	90/75 mg ^o	-
Vitamin E**	12 mg	15 mg	-
β-Carotene** and other carotenoids**	none	none	none

* + and **: For these footnotes refer to Table IV

^o males/females

** intakes of 3-6 mg/day of β-carotene from food sources are prudent to maintain plasma β-carotene concentrations associated with a lower risk of various chronic diseases outcome

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

Table IX: DRI values for **Adults (51 and older)**
(Dietary Antioxidants panel report 2000).

Nutrient	EAR	RDA	AI
Vitamin C*	75/60 mg ^o	90/75 mg ^o	-
Vitamin E**	12 mg	15 mg	-
β-Carotene ⁺⁺ and other carotenoids ^{**}	none	none	none

*+ and **: For these footnotes refer to Table IV

^o males/females

⁺⁺ intakes of 3-6 mg/day of β-carotene from food sources are prudent to maintain plasma β-carotene concentrations associated with a lower risk of various chronic diseases outcome

Special consideration for vitamin C:

Special consideration was given to smoking as a factor affecting vitamin C requirement. Smokers have lower vitamin C status than nonsmokers and data show that the metabolic turnover of ascorbate in smokers is about 35 mg/day greater than in nonsmokers, which is believed to be caused by increased oxidative stress and other metabolic differences. To obtain a near maximal steady-state ascorbic acid body pool equivalent to that of nonsmokers, smokers would require an additional 35 mg/day of vitamin C over the requirement by nonsmokers.

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 ULs could not be determined for any of the dietary antioxidant nutrients (vitamins C and E) because of lack of data and adverse effects in this 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 X: 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 Dietary Antioxidants in adults.

Vitamin	Criteria for NOAEL	Criteria for LOAEL	Comments
Vitamin C	No adverse effects known from food	Osmotic diarrhea and related gastrointestinal disturbances	Available data base does not show a causal relationship between excess vitamin C intake and other alleged adverse effects (kidney stone formation; excess iron absorption, reduced vitamin B ₁₂ plasma concentration and induction of vitamin B ₁₂ deficiency, systemic conditioning; pro-oxidant effects; allergic response)
Vitamin E	There is no evidence of adverse effects from consumption of vitamin E naturally occurring in food and from vitamin E added to food	Hemorrhagic effects were selected as the critical endpoint	Available human data fail to demonstrate consistently a causal association between excess α -tocopherol intake in normal, healthy individuals and any adverse health effect outcome In the absence of conclusive human data, the data set used to identify a LOAEL for vitamin E include studies showing increased hemorrhage toxicity in rats
β -Carotene and other carotenoids	There is no evidence of adverse effects from consumption of β -carotene or other carotenoids naturally occurring in foods	Data on the potential for β -carotene to increase the risk for lung cancer in chronic heavy smokers considered conflicting and not sufficient for a dose-response assessment and derivation of a LOAEL for this endpoint	Carotenodermia is considered more a cosmetic than an adverse effect and is readily reversible

Table XI: 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 Dietary Antioxidants in adults.

Dietary Antioxidant	NOAEL	UF₁	LOAEL	UF₂	UL for Adults
Vitamin C	2 g/day; estimated from LOAEL		3 g/day	1.5	2 g/day
Vitamin E	There is no evidence of adverse effects from consumption of vitamin E naturally occurring in food		500 mg/kg body weight/day determined on the basis of animal data	36	1000 mg/day
β-Carotene and other carotenoids	There is no evidence of adverse effects from consumption of β-carotene or other carotenoids naturally occurring in foods		Could not be set for β-carotene due to conflicting and not sufficient data for the parameter «increased risk of lung cancer in heavy chronic smokers»		none

Comments to Tables XI

Vitamin C

the NOAEL was estimated from the LOAEL under consideration of an uncertainty factor of 1.5. Due to the mild and reversible nature of osmotic diarrhea and related gastrointestinal disturbances no additional uncertainty factor (UF > 1) was considered necessary to determine the UL.

Vitamin E

The rather high uncertainty factor of 36 is considering several sources of uncertainty taking into account the extrapolation of LOAEL to NOAEL (UF = 2), extrapolation from subchronic to chronic intake (UF = 2), extrapolation from *animal* to human data (UF = 3), and interindividual variation in sensitivity (UF = 3). The combination of these various uncertainty factors yields an overall UF of 36 to extrapolate from the LOAEL in animals to derive a Tolerable Upper Intake Level UL for humans of 14 mg/kg body weight/day.

The resulting UL was multiplied by the average of the reference body weights for male and female adults, and rounded to 1000 mg/day. Since at high intakes all of the stereoisomers of α -tocopherol are considered equivalent given that all forms of vitamin E are absorbed, the UL of 1000 mg/day applies to *any form of vitamin E*.

The UL of 1000 mg/day is consistent with the limited human data base indicating oral intakes of up to 1100 to 2100 mg/day vitamin E to be without side effects. The UL for infants was judged *not determinable due to insufficient data*. Therefore, it is suggested that intake

for infants should be only from food and formula. There are no reports of vitamin E toxicity in children and adolescents and the UL for this group was adjusted on the basis of relative body weight.

β -Carotene and other carotenoids

No adverse effects other than carotenodermia have been reported from the consumption of β -carotene or other carotenoids in foods. These are considered harmless and are readily reversible when ingestion of high doses of carotenoids is discontinued.

There are no adverse effects reported when β -carotene is used therapeutically in doses up to 180 mg/day for the treatment of erythropoietic protoporphyria. Long-term intake/supplementation with β -carotene does not lead to hypervitaminosis A.

There is no evidence that β -carotene or other carotenoids are mutagenic, teratogenic, or carcinogenic in experimental animals.

The evaluation of an UL for β -carotene for the endpoint «increased risk of lung cancer in heavy chronic smokers» is based on the results from the ATBC Study, the CARET Study, and The Physicians' Health Study. These trials indicate a lack of evidence of overall benefit on total cancer or cardiovascular disease and possible harm in certain subgroups such as current chronic smokers or asbestos exposed subjects. The Panel concluded that an UL for β -carotene could not be evaluated due to the conflicting and not sufficient data for a dose-response assessment for the indicator “increased risk of lung cancer in heavy chronic smokers”.

The existing recommendation for consumption of five or more servings of fruits and vegetables per day is supported and this would

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

provide 3-6 mg/day of β -carotene. This advise does not pertain to the possible use of supplemental β -carotene as a pro-vitamin A source or for the prevention of vitamin A deficiency in populations with inadequate vitamin A nutriture or in patients suffering from erythropoietic protoporphyria.

Table XII: NOAEL, LOAEL, and UL for Dietary Antioxidants in adults (19-50 years)

Dietary Antioxidant	NOAEL	LOAEL	UL
Vitamin C*	2 g/day	3 g/day	2 g/day
Vitamin E*	Human data base insufficient	500 mg/kg body weight/day (valid for rats)	1000 mg/day any form of vitamin E
β -Carotene* and other carotenoids	No adverse effect from food sources	Inconsistent data for β -carotene	none

* see comments to Table XI

7. Reported dietary and supplement intakes of Dietary Antioxidants in the USA

Table XIII: Dietary and supplement intake for adults in the USA

Dietary Antioxidant	Dietary Intake mg/day		Supplement Intake mg/day	
	Men	Women	Men	Women
Vitamin C*	105	90	120+	90+
Vitamin E (as RRR- α -tocopherol)**	9.4	6.4	10.3+	7.3+
β -Carotene and other carotenoids ⁺⁺	2.9 β -carotene 2.2 lutein 2.3 lycopene ⁺⁺⁺	2.5 β -carotene 1.9 lutein 2.1 lycopene ⁺⁺⁺	no reliable data available	no reliable data available

* median intake

+ median total intake (dietary and supplements)

** estimates for vitamin E intake may be low due to underreporting of energy intake, difficulties in assessing fat and oil intake as a major carrier for vitamin E, uncertainties about the particular fats and oils influencing the relative content of vitamin E, and the small number of samples causing the vitamin E content of food sources to be very variable

++ data for intakes of carotenoids from the Third National Health and Nutrition Examination Survey (NHANES III) based on an expanded recent food composition database for carotenoids are currently being analyzed and will be included in the forthcoming DRI report that will deal with vitamin A (to be available January 2001)

+++ data from 1992 National Health Interview Survey; mean intakes/day

8. Results from the panel on Dietary Antioxidants and major perspectives

The overall recommendations can be summarized as follows:

- Recommendation for vitamin C was increased by nearly 50 % and additional intake was set for smokers (+35 mg/day)
- The EAR/RDA for vitamin E was solely based on (RRR)- α -tocopherol and expressed as mg. The formerly used tocopherol-equivalents were abandoned.
- The recommended RDA was about doubled to the former value (8-10 mg α -tocopherol equivalents to 15 mg (RRR)- α -tocopherol)
- High intakes of PUFA should be accompanied by increased vitamin E intakes
- The scientific basis for the dietary antioxidants was evaluated for their risk reduction potential of certain chronic diseases (cardiovascular disease; certain cancers; eye disease). There is an increasing acceptance of the potential role of vitamins C and E in cardiovascular disease, and the risk reduction of prostate cancer by vitamin E. Data were considered promising but more data are required on the respective endpoints and relevant selected biomarkers.
- β -carotene was not recognized as an *in vivo* antioxidant, and no DRIs were established due to an inconclusive science base. Supplements containing β -carotene are considered not advisable for the general population except as source of vitamin A and for prevention of and control of vitamin A deficiencies in at risk populations. The Panel dealing with vitamin A is to define the conversion rate of β -carotene into vitamin A.
- Prudent intake levels of β -carotene from food of 3-6 mg/day are proposed to attain plasma levels associated with lower risk of various chronic diseases
- Encourage generous intakes of fruits and vegetables rich in carotenoids
- For all dietary antioxidants no EAR/RDA set for infants, rather than an AI due to lack of data; data were derived from extrapolation of recommendations for adults on a body weight basis or calculated from human milk intake by exclusively breast-fed infants
- Data on the variability of the requirement to calculate a standard deviation were considered to be insufficient for all assessed dietary antioxidants and therefore a coefficient of variation of 10 % was generally used
- The Panel clearly indicated that there is no scientific evidence that even very large intakes of vitamin C cause adverse health effects. Specifically, in healthy individuals vitamin C does not cause mutations, cancer, hardening of arteries, kidney stones, pro-oxidant effects, excess iron absorption, vitamin B₁₂ deficiency, or allergic reactions. The Panel used osmotic diarrhea and gastrointestinal disturbances as the criteria to determine the upper tolerable level of intake (UL) for vitamin C at a daily intake of 2000 mg/day.
- For vitamin E a tolerable upper level of intake (UL) for adults of 1'000 mg/day expressed by weight of any supplementary form (natural or synthetic) of α -tocopherol was set based on animal data and application of a rather high uncertainty factor of 36, considering several sources of uncertainty (LOAEL to NOAEL, subchronic results to chronic results, translation from animal data to humans, interindividual variation in sensitivity). The Panel report stated that oral intakes of vitamin E at doses up to 2100 mg α -tocopherol daily have not been associated with any adverse effects in humans.
- No tolerable upper level of intake for β -carotene was set due to the fact that no adverse effects have been observed other than in two intervention studies in long-term heavy chronic smokers. The Panel, however, considered the data in smokers conflicting and insufficient for setting a Tolerable Upper Level of Intake (UL) for β -carotene. Yellowing of the skin with intakes of 30 mg/day was not considered an adverse effect, since it is easily reversible and harmless.

9. Dietary Antioxidant panel recommendation for future research

The FNB Panel has 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 C

- Knowledge of vitamin C intakes needed to fulfill specific functional roles of ascorbate is requested to allow for a more accurate and precise determination of the individual and average population requirement of vitamin C
- Development of more reliable tests for in vivo oxidative damage and for the further understanding of interactions of ascorbate with other physiological antioxidants are asked for in order to be able to determine vitamin C requirement based on antioxidant function
- Priority should be given to large-scale studies using state-of-the-art biomarkers for setting Estimated Average Requirements (EAR) for children, adolescents, pregnant or lactating women, and the elderly
- Population studies on the relationship of vitamin C nutriture and chronic disease should focus more on the individuals or populations who eat few fruits and vegetables or are marginally deficient in vitamin C
- Eventual studies with high doses should be designed in a way to provide data on potential adverse effects (e.g. pro-oxidant effects on iron-ascorbate couple)

Vitamin E

- Evaluate biomarkers for the assessment of vitamin E intake and status
- Priority should be given to large-scale studies using state-of-the-art biomarkers for setting Estimated Average Requirements (EAR) for children, adolescents, pregnant or lactating women, and the elderly
- Better and more valid estimates for vitamin E intakes from foods, especially the vitamin E content of fats and oils, are needed
- Information on the relationship between oxidative stress and vitamin E status is needed
- Pharmacokinetic studies on the fate of vitamin E (turnover data, information on various pool sizes; major metabolites etc) are requested and their potential role in estimating requirement
- More information is needed on the mechanism of vitamin E function (e.g. antioxidant function; specific modes of action; mechanism of tissue regulation)
- Additional data from on-going intervention studies on the preventive potential of vitamin E (cardiovascular disease; prostate cancer)
- Information on other forms of vitamin E and their potential biological role in humans (e.g. γ -tocopherol as nitric oxide scavenger; metabolic fate of γ -tocopherol)

β -Carotene and other Carotenoids:

- α -carotene and other carotenoids have been shown to modulate a variety of intermediate endpoints (macular pigment optical density as a promising intermediate marker for age-related macular degeneration). Validation of these endpoints are needed in human prospective studies.

10. References

- Studies on the effect of long-term depletion of β -carotene and subsequent repletion and evaluation of validated intermediate endpoints
 - Additional data are needed from long-term intervention trials involving β -carotene, including examination of health effects in populations with varying baseline risk profiles
 - Additional research is needed targeting the putative mechanisms to explain a possible increase in lung cancer risk in heavy chronic smokers taking long-term high-dose β -carotene supplements
 - Post-trial follow-up of completed β -carotene trials (ATBC, CARET, Physicians' Health Study, LINXIAN Study)
 - Data on dietary intake of individual food carotenoids from large, representative population samples, including intakes from supplements
 - Studies to evaluate equivalency and demonstrate efficacy of carotenoids in foods to meet the vitamin A requirement in vitamin A-deficient populations
 - Studies on health effects of dietary carotenoids other than β -carotene (potential association between lycopene and decreased prostate cancer risk, between lutein/zeaxanthin and lower risk of age-related macular degeneration, between α -carotene or lutein and various cancers)
- (1) Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. A report by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Vitamin C, Vitamin E, Selenium, and Carotenoids; Food and Nutrition Board, Institute of Medicine, National Academy Press, Washington, D.C., 2000 (<http://www.nap.edu>)
 - (2) Pre-publication: 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., 2000 (<http://www.nap.edu>)



Vitamins

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