Vitamin E

Common Acronyms

CNS	Chinese Nutrition Society
CRN	Council for Responsible Nutrition
DRI	dietary reference intake
EC SCF	European Commission Scientific Committee on Food
EFSA	European Food Safety Authority
EVM	Expert Group on Vitamins and Minerals
ICMR-NIN	Indian Council of Medical Research - National Institute of Nutrition
IOM	Institute of Medicine
IU	international unit
KNS	Korean Nutrition Society
LOAEL	lowest observed adverse effect level
NDA	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NOAEL	no observed adverse effect level
RCT	randomized clinical trial
SUL	safe upper level
UF	uncertainty factor
UL	tolerable upper intake level

Introduction

Vitamin E is a complex substance that comes in eight forms differentiated by the methyl groups on their chromanol ring structure: alpha-tocopherol, beta-tocopherol, gamma-tocopherol, delta-tocopherol, and the esters of each. Alpha-tocopherol ester is the most common form used in manufactured foods and supplements and is the only vitamer recognized to be bioactive and essential in humans (Higdon 2004; EFSA 2024). Eight potential stereoisomers of alpha-tocopherol are determined by the configuration (R or S) at each of its three stereogenic centers (at the 2, 4', and 8-positions). Plant-derived alpha-tocopherol has an RRR configuration and is referred to as "*RRR* alpha-tocopherol", whereas synthetic alpha-tocopherol is referred to as *all-racemi(rac)*-alpha-tocopherol (Higdon 2004; EFSA 2015, 2024). There are equal numbers of a

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closely related group of vitamins called tocotrienols. Their chemical forms (alpha, beta, gamma, and delta, and their esters) are closely analogous (but not identical) with tocopherols. Together, these tocopherols and tocotrienols are referred to as tocochromanols; however, tocotrienols are not included in this chapter.

Vitamin E's main role is that of an antioxidant and a scavenger of free radicals, making it effective as a protector of the integrity of lipids and phospholipid membranes. As an antioxidant, vitamin E is strongly interactive with other dietary systemic antioxidants, such as vitamin C and glutathione and several enzyme systems, such as glutathione reductase and superoxide dismutase. Vitamin E has been shown to be essential to human health; for example, one of the earliest observations of the physiological effects of vitamin E deficiency relates to reproduction. In deficiency models, fetuses died and were resorbed in females and the testes became atrophied in males. Indeed, the chemical name for vitamin E, tocopherol, is related to this protective effect on reproduction (Nelson 1980).

Safety Considerations

Vitamin E has been shown to have a wide margin of safety (Bendich and Machlin 1988; Dickinson 2002; Higdon 2004; EFSA 2015; Xiong et al. 2023). The scientific literature contains many reports of safe, continuous intake of vitamin E supplements at levels that are many multiples of the current RDA of 15 mg per day alpha-tocopherol (IOM 2000). The evidence comes from different types of studies, ranging from observational studies of a few subjects to large randomized, controlled trials looking for interventional impacts on cancer, cardiovascular disease, and other disorders. There have been dozens of published studies with documented safety observations for vitamin E supplements. Approximately 75 human clinical trials published since the 3rd edition of the book (i.e., starting in 2014) were identified that met the inclusion criteria for the current update. A full literature review is outside the scope of this chapter; therefore, only studies identified in the updated search with vitamin E intake levels greater than 1,000 IU per day, and therefore pertinent to assessing a revised UL based on CRN's methodology, are summarized below together with key studies already summarized in the 3rd edition.

Gillilan et al. (1977). In a double-blind crossover study by Gillilan and colleagues, 48 patients with stable angina documented by electrocardiography and angiography were randomly assigned to receive vitamin E at 1,600 IU per day for 6 months, either before or after a 2-month placebo period. Although vitamin E did not appear to improve the symptoms or exercise capacity of these patients with well-established heart disease, no adverse effects were observed. The patients showed no differences in symptomatic or laboratory indices of heart disease between the active therapy and placebo periods.

Meydani et al. (1998). Meydani and colleagues conducted an extensive 4-month safety study of vitamin E at 60, 200, or 800 IU per day in 88 healthy elderly persons. None of the subjects reported any side effects, nor did they show any abnormalities on a wide array of laboratory tests that studied plasma proteins and lipids; glucose; lipoproteins; bilirubin and other parameters of liver, kidney, and metabolic function; red blood cell counts; bleeding time and other parameters of coagulation; and a wide range of immune function indicators.

Cambridge Heart Antioxidant Study (CHAOS) (Stephens et al. 1996). The safety findings from the relatively small trials by Gillilan et al. and Meydani et al. were corroborated by the larger Cambridge Heart Antioxidant Study (CHAOS), in which 2,002 patients were randomized to receive a placebo or vitamin E at 400 or 800 IU per day. Over a median follow-up of 510 days, no significant adverse effects of vitamin E supplementation were reported among these patients with symptomatic and angiographic coronary disease. Indeed, the rate of treatment discontinuation stemming from adverse effects—a common gauge of patient tolerance—was only 0.55 percent for the entire population, with no difference between the actively treated and control patients.

Heart Outcomes Prevention Evaluation Study (HOPE Study Investigators 2000). The Heart Outcomes Prevention Evaluation (HOPE) study was an evaluation of the angiotensin-converting enzyme (ACE) inhibitor, ramipril and/or 400 IU per day of vitamin E per day in 9,541 patients with multiple cardiovascular risk factors. According to the HOPE investigators, “Vitamin E was well tolerated, with no significant adverse events

as compared with placebo" over the mean follow-up of 4.5 years.

Roche European American Cataract Trial (REACT) (Chylack et al. 2002). Nor was vitamin E safety an issue in the Roche European American Cataract Trial (REACT), in which 297 patients with age-related cataracts were randomized to receive a placebo or an antioxidant cocktail containing vitamin E at 600 mg per day along with vitamin C and beta-carotene, a nutrient that is a biochemical precursor to vitamin A. In this trial, 78 percent of the patients were followed for 2 years, 53 percent for 3 years, and 12 percent for 4 years.

Age-Related Eye Disease Study (AREDS) (Age-Related Eye Disease Study Research Group 2001). The 3,640 patients with vision loss or eye lesions who were being seen at retinal diseases clinics in the Age-Related Eye Disease Study (AREDS) were also randomized into placebo or antioxidant-cocktail groups; additionally, zinc supplementation was compared with a placebo. The patients took the cocktail—which contained 400 IU vitamin E as well as vitamin C and beta-carotene—daily for a mean of 6.3 years. The AREDS researchers singled out a significant increase in skin yellowing—a classic sign of high beta-carotene intake—as the only notable apparent side effect of antioxidant therapy.

Brown and Colleagues (Brown et al. 2001; Cheung et al. 2001). Brown and colleagues tested the combination of simvastatin and niacin, with or without an antioxidant cocktail containing vitamin E at 800 IU per day, against either the cocktail alone or matching placebos in 160 patients with clinical coronary disease, low levels of high-density-lipoprotein (HDL) cholesterol, and normal levels of low-density-lipoprotein (LDL) cholesterol. No adverse effects were observed in patients who received antioxidants alone, but there was an unexpected blunting of the favorable HDL-elevating response to simvastatin-niacin in those who received antioxidants plus the drug treatments.

DATATOP (Parkinson Study Group 1998). The DATATOP clinical trial, which followed 800 subjects for 8.2 years, found no adverse effects of 2,000 IU of vitamin E per day. This study supports the safety of very high intakes of vitamin E over a long period.

Devaraj et al. (2007). The long-term safety of vitamin E is also supported by this randomized, controlled, double-blind trial published by Devaraj and colleagues. The authors concluded supplementation with 1,200 IU *RRR* alpha-tocopherol per day for two years in patients with cardiovascular disease to be safe.

Khatami et al. (2016). More recently, no adverse effects were reported in patients with diabetic neuropathy supplemented with 1,200 IU vitamin E per day for 12 weeks.

Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study (ATBC 1994). Against this backdrop of multiple observational and prospective, randomized trials suggesting excellent safety for vitamin E supplementation stands the ATBC Cancer Prevention Study, which raised a flag of caution. Among 29,133 male smokers in Finland, ages 50 to 69 years, vitamin E ingested at 50 mg per day for 5 to 8 years was associated with a 7.8 percent rate of death from hemorrhagic stroke, compared with a 5.2 percent rate for the placebo (66 cases in the vitamin group, compared with 44 in the controls). The authors did not discuss the nearly significant decrease in occlusive stroke, a much larger group than those with hemorrhagic stroke. Overall, there was a nearly significant decrease in total strokes. As with many antioxidants, care must be exercised when exogenous factors are already compromising the health status, which, besides the smoking mentioned above, also includes concomitant use of pharmaceuticals (Hemilä and Kaprio 2011; Rutkoswki and Grzegorczyk 2012).

In the ATBC study vitamin E was also associated with a lower incidence of prostate cancer and reduced mortality from ischemic stroke and ischemic heart disease. But no degree of statistical significance was provided for any of these apparent differences. The authors concluded only that the observation of a higher hemorrhagic stroke mortality with vitamin E "requires careful review." Such careful review has since occurred and has confirmed the available body of evidence on hemorrhagic stroke to be insufficient for utility in the derivation of an UL for vitamin E (discussed further below). In addition, the IOM (2000) report that delineated the DRI values for vitamins E and C concluded that the "preliminary"

ATBC findings were "not convincing" in the absence of corroboration in other large-scale clinical trials.

The associations between vitamin E (alpha-tocopherol) intake and some potential adverse outcomes previously identified in studies – e.g., all-cause mortality, prostate cancer, cardiovascular outcomes, and impaired blood coagulation and bleeding – have recently been reviewed and assessed by EFSA (2024). Following its review of the available systematic reviews and meta-analyses of RCTs, the EFSA Panel determined the available evidence regarding all-cause mortality to be insufficient for deriving an UL for vitamin E. Similarly, the EFSA Panel conducted its own systematic review of available RCTs, observational studies in humans, and animal toxicology data related to increased risk of prostate cancer; the Panel determined the evidence to be insufficient to conclude an association with vitamin E intake.

Based on its preliminary scoping review, the EFSA (2024) Panel identified several cardiovascular endpoints to assess based on systematic review of intervention and observational human studies, including morbidity and mortality related to myocardial infarction and angina, ischemic and hemorrhagic stroke, and congestive heart failure. The Panel considered that the available data do not suggest a positive relationship between the intake of alpha-tocopherol and an increased risk of cardiovascular disease (composite endpoint), coronary heart disease (including myocardial infarction or angina), stroke (composite endpoint), or ischemic stroke. Regarding hemorrhagic stroke and congestive heart failure, the EFSA Panel determined that the available evidence cannot be used for deriving an UL for vitamin E. The available trials investigating these two outcomes were generally concluded by EFSA to provide no evidence for an adverse effect or were conducted in a patient population that should be excluded from the target population for a UL.

The human literature contains a few reports, in addition to that of the ATBC trial, that tentatively associate bleeding complications with vitamin E supplementation. Such reports sometimes involve persons with vitamin K deficiency, especially in conjunction with chronic anticoagulant therapy, such as warfarin (Coumadin) or high-dose aspirin. In addition, increased risk of bleeding, hemorrhage, and prolonged prothrombin times (PT) and activated partial thromboplastin times (aPTT) have been reported in some studies with animal models. These

associations have led some reviewers to recommend caution and observation in patients on taking both vitamin E supplements and long-term warfarin (Spencer 2000). More recently, based on systematic review of the body of evidence in populations not taking anticoagulant or antiplatelet medications, the Panel (2024) concluded "that no relevant data were retrieved regarding the risk of bleeding events with α-tocopherol supplementation in human intervention studies" and "that PT and aPTT were not affected by α-tocopherol supplementation (546–804 mg/day α-tocopherol for 2–12 weeks)". This conclusion is further supported in a clinical trial not cited by EFSA (2024), in which 1,200 IU per day for 14 days of a gamma-tocopherol-enriched supplement had no effect on blood coagulation parameters. Nevertheless, the EFSA Panel identified the effect of vitamin E on blood clotting and the increased risk of bleeding as the critical effect to establish its UL, stating that the mechanisms by which alpha-tocopherol "could impair blood clotting could be similar in animals and humans".

It has been suggested that high intake of vitamin E may influence coagulation in some persons with vitamin K deficiency, but not in those persons with adequate vitamin K levels—in other words, the overwhelming majority of the population (Corrigan and Ulfers 1981; Corrigan 1982; Kappus and Diplock 1992; Dowd and Zeng 1995). Indeed, a large trial of patients on long-term warfarin who also took 800 to 1,200 mg of vitamin E showed no changes in coagulation parameters that would suggest an increased bleeding risk (Kim and White 1996). Of note, the EFSA (2024) Panel concluded that "excess intake of α-tocopherol (and other tocochromanols) may affect vitamin K status".

Official Reviews

IOM (2000). The IOM reviewed all data relevant to vitamin E safety but did not identify a human NOAEL or LOAEL. Instead, it identified a LOAEL of 500 mg per kg per day from animal data and calculated a human UL by applying a composite UF of 36. Assuming a body weight of 68.5 kg and rounding off the value, the calculated UL is 1,000 mg per day for adults. Although the different chemical forms of vitamin E have different potencies (that is, IU per mg) for beneficial effects, the IOM concluded that potency for potential adverse effects is not known to vary in an analogous manner, and therefore the IOM did not differentiate between *all-rac* and

RRR alpha-tocopherol with regard to possible adverse effects. Hence, the IOM applied a uniform UL value to all forms of vitamin E.

EFSA (2024). Previously, EC SCF (2003) reviewed all the evidence and found no adverse effects for oral vitamin E in humans. Declaring the evidence at higher intakes to be insufficient, the EC SCF selected the clinical study by Meydani and colleagues (1998) to identify a NOAEL of 800 IU per day, or approximately 540 mg per day. Judging the database to be only moderately robust, the EC SCF applied a UF of 2, converting from IU to mg to derive a UL of 270 mg per day, rounded up to 300 mg per day. In 2024, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) published its scientific opinion on the UL for vitamin E, limiting its evaluation to alpha-tocopherol on the basis that it is the only essential form of vitamin E. Following its assessment, including systematic review of the risks associated with alpha-tocopherol and impaired blood coagulation and bleeding, cardiovascular outcomes, and prostate cancer, the Panel identified effects on blood clotting and increased risk of bleeding as the critical effect for risk assessment. The Panel concluded that "no relevant data were retrieved regarding the risk of bleeding events with α-tocopherol supplementation in human intervention studies", but selected this critical endpoint, stating that the mechanisms by which alpha-tocopherol "could impair blood clotting could be similar in animals and humans". The clinical study by Meydani et al. (1998), supported by additional studies, was maintained as the basis of the EFSA UL. The Panel concluded that no change to the previous UL of 300 mg alpha-tocopherol per day in adults was warranted; however, the EFSA UL is not applicable to those on anticoagulant and antiplatelet medications, secondary prevention for cardiovascular disease, or with vitamin K malabsorption syndromes.

Expert Group on Vitamins and Minerals (EVM 2003). The UK's EVM identified an SUL range of 800 to 1600 IU based on the Meydani and Gillilan studies (Gillilan et al. 1977; Meydani et al. 1998) and then used the more conservative value of 800 IU value to calculate a vitamin E SUL of 540 mg per day.

Chinese Nutrition Society (CNS 2023). An UL value for vitamin E of 700 mg per day in adults was set by the CNS.

Indian Council of Medical Research - National Institute of Nutrition (ICMR-NIN 2020). The ICMR-NIN determined the UL for vitamin E in adults to be 1,000 mg per day, noting this value to be "in line with international recommendations" and citing IOM (2001) and the 3rd edition of the CRN book.

Korean Nutrition Society (KNS 2020). The KNS published its general approach to evaluating data for setting DRI values. Based on this approach, UL values of 540 and 500 mg alpha-TE per day were derived for vitamin E in adults ages ≥19 and 18 years, respectively.

CRN Recommendations

The goal of the current update to CRN's supplemental UL for vitamin E was to determine whether more recent human clinical data are available that might impact the conclusions published in the 3rd edition. While not all human clinical trials are specifically designed to evaluate adverse effects, no new trials were identified following CRN's updated methodology that reported blood coagulation or bleeding-related symptoms, or other serious adverse effects associated with vitamin E intervention. As with any assessment in which not all available data are reviewed, inherent uncertainties with the risk assessment and selection of the UL are recognized. As discussed above, other methodologies have been used by some government agencies to derive associated UL values for vitamin E and were based on more conservative human clinical trial and/or animal toxicology data.

CRN's safety methodology for deriving a supplemental intake UL prioritizes data from human studies, when available. The table below summarizes the key human studies considered in deriving an updated UL for supplemental intakes by CRN according to its principal points of departure for risk assessment (as described in the Methods).

Key Studies Considered for the CRN UL for Vitamin E

Reference	Study Design	Participant Description	No. of Subjects	Dose(s) (IU/day)	Duration	NOAEL (IU/day)	LOAEL (IU/day)
Key studies from 3rd edition							

Anderson and Reid 1974	Double blind clinical trial	Patients with angina pectoris	38	3,200	9 weeks	3,200	N/A
Gillilan et al. 1977	Double blind clinical trial	Patients with stable angina	48	1,600	6 months	1,600	N/A
Meydani et al. 1998	Double blind clinical trial	Healthy volunteers	88	60, 200, or 800	4 months	800	N/A
Parkinson Study Group 1998	Double blind clinical trial	Patients with early Parkinson's disease	800	2,000	8.2 years[a]	2,000	N/A
Key studies identified in update							
Devaraj et al. 2007	Double blind clinical trial	Patients with coronary artery disease	90	1,200	2 years	1,200	N/A
Khatami et al. 2016	Double blind clinical trial	Patients with diabetic neuropathy	60	1,200	12 weeks	1,200	N/A

N/A, not applicable
[a] Average across study population

CRN identifies a vitamin E NOAEL of 1,600 IU from clinical trial data that showed no adverse effects at this level of intake (Gillilan et al. 1977). CRN considers 1,600 IU as the upper limit to have a very low level of uncertainty because of the absence of adverse effects at the higher daily intakes of 2,000 IU for an average of 8 years (Parkinson Study Group 1988) and 3,200 IU for nine weeks (Anderson and Reid 1974). This approach differs from that employed by the recent EFSA (2024) Panel review, which conservatively selected the Meydani et al. (1988) study, as it assessed and demonstrated a lack of adverse effects on parameters specific to the critical endpoint identified by the Panel.

To simplify safety considerations of different forms of vitamin E and yet reach appropriately cautious conclusions, CRN recommends conversion of the IU to mg alpha-tocopherol equivalents (alpha-TE). Because most clinical trials have been conducted with *all rac*-alpha-tocopheryl acetate, conversion of a UL for supplements in IU to the corresponding vitamin E activity in mg alpha-TE will result in a more conservative UL. With the conversion to mg alpha-TE (i.e., 1 IU *RRR* alpha-tocopherol being equivalent to 0.67 mg), the NOAEL of 1,600 IU is equivalent to 1,073 mg vitamin E per day. As described in the Methods, if the supplemental intake dose-response relationship is identified from the strongest data and assessed conservatively, no additional uncertainty factor is needed (that is, the implicit UF is 1.0). Consistent with CRN's methodology, an UF of 1 is applied to yield a UL of 1,073 mg vitamin E per day (rounded down to 1,000 mg per day) for adults, a value very similar to that identified by

the IOM through extrapolation from animal data. In addition, while the studies conducted at higher doses did not specifically evaluate parameters related to risk of bleeding (Anderson and Reid 1974; Gillilan et al. 1977; Parkinson Study Group 1988), the EFSA (2024) Panel systematically reviewed available human studies and concluded there to be no indications of effects of α-tocopherol supplementation on PT and aPTT at doses between 546 mg per day and 804 mg per day.

The CRN UL for vitamin E of 1,000 mg per day for supplements applies to healthy adults who are not taking any anticoagulant or antiplatelet drug. CRN notes that available data suggest alpha-tocopherol at high doses may affect vitamin K status (EFSA, 2024); individuals with known risk factors related to vitamin K absorption should consult with their healthcare provider.

Quantitative Summary for Vitamin E for Adults

CRN (2024) UL, supplemental intake	1,000 mg (1600 IU)/day[a]
IOM (2000) UL, total intake	1,000 mg/day
EFSA (2024) UL, total intake	300 mg/day
EVM (2003) SUL, supplemental intake	540 mg (800 IU)/day[b]
CNS (2023), total intake	700 mg alpha-TE/day
ICMR-NIN (2020), total intake	1,000 mg/day
KNS (2020), total intake	540 mg alpha-TE/day (500 mg alpha-TE/day for ages 15-18 years)

[a] Applies to healthy adults who are not taking any anticoagulant or antiplatelet drug. Individuals with known risk factors related to vitamin K absorption should consult with their healthcare provider.
[b] Not applicable to those on anticoagulant and antiplatelet medications, secondary prevention for cardiovascular disease, or with vitamin K malabsorption syndromes.

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