

Vitamin E

Function

Unlike several other vitamins, vitamin E has not yet been shown to be directly associated with the function of any enzyme system (Sokol 1996). Its only firmly established 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. Accumulating evidence suggests that vitamin E may have several other functions, including modulation of gene expression and inflammatory response.

Animals deficient in vitamin E experience a progressive necrosis of the muscles and nervous system. One of the earliest observations of the physiological effects of vitamin E deficiency relates to reproduction. In deficiency models in female animals, their fetuses die and are resorbed; in males, the testes become atrophied. Indeed, the chemical name for vitamin E, tocopherol, is related to this protective effect on reproduction.

In addition to the effects that make vitamin E nutritionally essential, numerous scientific reports, which include mechanistic data (Sies and Stahl 1995), epidemiology (Knekt et al. 1991), and some human intervention clinical trials (Jialal and Devaraj 2003), support the hypothesis that vitamin E is associated with a decreased risk of heart disease and certain cancers (Stephens et al. 1996; Food and Nutrition Board 2000). Clinical trials, however, have produced mixed results on whether vitamin E protects against heart disease and cancer (Dickinson 2002, Jialal and Deveraj 2003).

Safety Evidence

The scientific literature contains many reports of safe continuous intake of vitamin E supplements at levels that are many multiples of the RDA. The evidence comes from different types of studies, ranging from observational studies of a few subjects to large randomized, controlled intervention trials looking for effects on cancer, cardiovascular disease, and other disorders. There have been more than twenty published studies with documented safety observations for vitamin E supplements, involving a total of more than 80,000 people.

In a double-blind crossover study by Gillian and his colleagues, forty-eight patients with stable angina documented by electrocardiography and angiography were randomly assigned to receive vitamin E at 1,600 IU per day for six months,

either before or after a two-month placebo period (Gillian et al. 1977). Although vitamin E did not appear to improve the symptoms or exercise capacity of these patients with well-established heart disease, it did prove entirely safe. The patients showed no differences in symptomatic or laboratory indices of heart disease between the active therapy and placebo periods.

Meydani and her colleagues conducted an intensive four-month safety study of vitamin E at 60, 200, or 800 IU per day in eighty-eight healthy elderly persons (Meydani et al. 1998). 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.

The safety findings from these two small trials 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 (Stephens et al. 1996). 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.

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 in 9,541 patients with multiple cardiovascular risk factors (HOPE 2000). 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.

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 (Chylack et al. 2002). In this trial, 78 percent of the patients were followed for two years, 53 percent for three years, and 12 percent for four years.

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 to a placebo (AREDS 2001). 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 coworkers 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 (Brown et al. 2001; Cheung et al. 2001). 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.

The DATATOP clinical trial, which followed 800 subjects for 8.2 years, found no adverse effects of 2000 IU of vitamin E per day (Parkinson Study Group 1998). This study supports the safety of very high intake of vitamin E over a long period.

Against this backdrop of multiple observational and prospective, randomized trials suggesting excellent safety for vitamin E supplementation stands the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study, which raised a flag of caution (ATBC 1994). Among 29,133 male smokers in Finland, aged fifty to sixty-nine years, vitamin E ingested at 50 mg per day for five to eight years was associated with a 7.8 percent rate of death from hemorrhagic stroke, as compared to a 5.2 percent rate for the placebo (sixty-six cases in the vitamin group, compared to forty-four in the controls). On the other hand, 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 occurred; in a further evaluation, these same researchers concluded that “alpha-tocopherol supplementation increases the risk of fatal hemorrhagic strokes but prevents cerebral infarction” (Leppala et al. 2000). In this study, within three months of the initial stroke diagnosis there were eighty-five deaths from subarachnoid hemorrhagic stroke, with the group supplemented by vitamin E seeing twenty-eight more such deaths, or 50 percent more, than the control group. By contrast, the 807 deaths from cerebral infarction suffered by those with vitamin E supplementation represented fifty-three fewer deaths, or a decrease of 14 percent when compared to the group that was not taking vitamin E supplements. The overall net effect of vitamin E on incidence of and mortality from strokes was statistically non-significant, but the numbers of stroke deaths were actually lower with vitamin E treatment.

The literature contains a few reports, in addition to that of the ATBC trials, that tentatively associated bleeding complications with vitamin E supplementation. Such reports sometimes involve persons with vitamin K deficiency, especially in conjunction with chronic anticoagulant therapy. These associations have led some reviewers to recommend caution and observation in patients on taking both vitamin E supplements and long-term warfarin.

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 et al. 1981; Kappus and Diplock 1992; Dowd 1995). Indeed, a recent 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). Vitamin E may also affect coagulation through its actions on platelets. Also, high levels of vitamin E inhibit protein kinase C and consequently the ability of platelets to clot (Freedman et al. 1996). The platelet effect could also generate beneficial effects of intakes of vitamin E.

The findings of the ATBC trial had little impact on the establishment of the FNB UL. The FNB report that delineated the Dietary Reference Intake (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 (Food and Nutrition Board 2000).

Published Official Reviews of Vitamin E Safety

The FNB reviewed all data relevant to vitamin E safety, but did not identify a human NOAEL or LOAEL (Food and Nutrition Board 2000). Instead, it identified a LOAEL of 500 mg per kg per day from animal data and calculated a human UL by applying a composite uncertainty factor 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/mg) for beneficial effects, FNB concluded that the potency for potential adverse effects is not known to vary in an analogous manner, and therefore FNB did not differentiate between *all-rac* and *RRR* α -tocopherol with regard to possible adverse effects. Hence, FNB applied a uniform UL value to all forms of vitamin E.

The EC SCF reviewed all the evidence and found no adverse effects for oral vitamin E in humans (Scientific Committee on Food 2003). Declaring the evidence at higher intakes to be insufficient, EC SCF selected the clinical study

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by Meydani and colleagues (Meydani et al. 1998) to identify a NOAEL of 800 IU per day. Judging the database to be only moderately robust, EC SCF applied a UF of 2, converting from IU to mg to derive a UL of 300 mg per day.

The UK EVM identified an SUL range of 800 to 1600 IU, then used the 800 IU value to calculate a vitamin E SUL of 540 mg (Expert Group on Vitamins and Minerals 2003).

CRN ULS (OSL Method) for Vitamin E

To simplify safety consideration of different forms of vitamin E and yet reach appropriately cautious conclusions, CRN recommends conversion of the IU to mg α -TE. Because most clinical trials have been conducted with synthetic *dl*- α -tocopheryl acetate (that is, *all rac*- α -tocopheryl acetate in the currently accepted scientific nomenclature), conversion of a ULS in IU to the corresponding vitamin E activity in mg α -TE will result in a more conservative UL. CRN identifies an OSL of 1,600 IU from clinical trial data that showed no adverse effects at this level of intake (Gillian et al. 1977). Correspondingly, CRN considers 1,600 IU, as the ULS, to have a very low level of uncertainty because of the absence of adverse effects at the higher intake of 3,200 IU (Anderson and Reid 1974). With the conversion to mg α -TE as performed by UK EVM, the CRN ULS of 1,600 IU is equivalent to 1,073 mg, a value very similar to that identified by FNB through extrapolation from animal data.

Comparison of Safety Values for Vitamin E

CRN ULS (OSL method)	1,000 mg (1,600 IU) (1,073 mg as RRR- α -tocopherol rounded off to 1,000 mg)
US FNB UL	1,000 mg
EC SCF (800 IU \div 1.5 \div 2)	300 mg (rounded up from 270 mg)
EC supplement maximum	Not established (as of May 2004)
UK EVM SUL (NOAEL 800—1,600 IU)	540 mg (800 IU, low end of NOAEL range; UF = 1)

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