Vitamin E

Introduction

Vitamin E is a complex substance that comes in eight forms: 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, while gamma-tocopherol is the most common form in the natural food supply (though the most common form can vary by geographic region) (Traber 2006). It is undetermined whether there are differences in health benefits among these different forms. There are equal numbers of a 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, but tocotrienols are not included in this chapter because there is comparatively little research available on them.

Vitamin E's only known 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. Unlike other vitamins, vitamin E has not yet been shown to be directly associated with the function of any enzyme system (Sokol 1996). 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. The most common test for vitamin E deficiency is the hemolysis of erythrocytes in vitro under the influence of hydrogen peroxide. In test systems commonly used alpha-tocopherol is the most potent, but the amounts of the gamma form far exceed the alpha forms in oils, such as soybean oil. Therefore, their relative importance as dietary antioxidants is uncertain (Institute of Medicine [IOM] 2000; Traber and Manor 2012).

Vitamin E has been shown to be essential to human health in several ways. One of the earliest observations of the physiological effects of vitamin E deficiency relates to reproduction. In deficiency models in female animals, their fetuses died and were resorbed; in males, the testes became atrophied. Indeed, the chemical name for vitamin E, tocopherol, is related to this protective effect on reproduction (Nelson 1980). In addition, numerous scientific reports, which include mechanistic data (Sies and Stahl 1995), epidemiology (Knekt et al. 1991), and some

human intervention clinical trials, support the hypothesis that vitamin E is associated with a decreased risk of heart disease and certain cancer. Clinical trials overall, however, have produced mixed results on whether vitamin E protects against heart disease and cancer. In summary, vitamin E is clearly essential and may reduce the risk of some chronic diseases, and it has a wide margin of safety (Bendich and Machlin 1988; Dickinson 2002; Higdon 2004).

Safety Considerations

The scientific literature contains many reports of safe continuous intake of vitamin E supplements at levels that are many multiples of the current 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 dozens of published studies with documented safety observations for vitamin E supplements, involving a total of more than 100,000 people.

Gillilan et al. (1977). In a double-blind crossover study by Gillilan and his 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, 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 et al. (1998). Meydani and her 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. Note that this interpretation by the authors did not stop the decisive inclusion of one narrow segment of these data in a meta-analysis of vitamin E intake and all-cause mortality (Miller et al. 2005), even though the "significant" endpoints were 1 of 23. The usual 5 percent probability threshold for significance is 1 of 20, so the 1 of 23 is well within the normal range of expectation based on random effects.

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 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. 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 on 800 subjects for 8.2 years, found no adverse effects of 2000 IU of vitamin E per day. This study supports the safety of very high intakes of vitamin E over a long period.

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 occurred; in a further evaluation, these same researchers concluded that "alpha-tocopherol supplementation increases the risk of fatal hemorrhagic strokes but prevents cerebral infarction" (Leppälä et al. 2000). In this study, within 3 months of the initial stroke diagnosis there were 85 deaths from subarachnoid hemorrhagic stroke, with the group supplemented by vitamin E seeing 28 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 53 fewer deaths, or a decrease of 14 percent, when compared with the group that was not taking vitamin E supplements. The overall net effects of vitamin E on incidence of and mortality from strokes were statistically nonsignificant, but the numbers of total stroke deaths were actually lower with vitamin E treatment.

The 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. 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).

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 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).

The findings of the ATBC trial have not altered the prevailing consensus that vitamin E intake up to the UL is safe. The IOM 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 (IOM 2000).

When stated in a misleading way, some comments can become self-fulfilling prophesies. For example, one paper is titled "no evidence supports vitamin E indiscriminate supplementation" (Dolan et al. 2009). At face value, this statement is true, but it is equally true for all substances. With the word "indiscriminate" included, the statement logically applies to everything: food, supplements, and drugs.

Meta-Analyses Studies. Meta-analysis is the combination of data from multiple studies to increase the total number of subjects being considered—that is, to increase the replication and statistical power, thus enabling the detection of small differences. At first glance, this would seem to be a great advance—that is, to increase the statistical power to detect small but real effects. And this would be true if two critical factors are appropriately considered and accounted for: (1) the statistical (mathematical) formulas must be appropriate and valid, and (2) the inclusion/exclusion criteria must be appropriate. Unfortunately, both aspects are commonly abused.

A prime example is the meta-analysis of high-dosage vitamin E supplementation reported by Miller and coworkers (2005). In this publication, the authors graphed the intake of vitamin E against the risk of "all-cause mortality." Lower intakes provided risk below the zero line (suggesting a protective effect) and at 400 IU or higher the risk line moved just above zero (suggesting adverse effects). For some unexplained reason, the authors changed the mathematical formula from a linear equation at low risk to a quadratic equation when the risk line was positive (above zero). Apparently, this was the only method that gave a statistically significant indication of harm by vitamin E. Even with this mathematical manipulation, the results indicated harm by vitamin E only if the WAVE trial (Women's Angiographic Vitamin and Estrogen Trial; Waters et al. 2002) was included—it indicated by far the highest risk of adverse effects by vitamin E in any trial. The meta-analysis authors made no note of the letters to

the editor that pointed out the shortcomings of the WAVE study—those researchers measured 22 different parameters and found 1 to be statistically elevated, and they made no mention of their 5 percent probability definition of "statistically significant." Thus, one would expect 1 of 20 parameters to be elevated on a random basis (1 of 20 is 5 percent). Without the WAVE trial data, meta-analysis would have shown nothing—even with the questionable statistical manipulations. In this example, the authors violated the principles of both critical criteria: (1) invalid statistical methods, and (2) inclusion regardless of the shortcomings of the clinical trial. Note that, in the WAVE study, the "significant" effects were 1 of 23 endpoints whereas 1 of 20 would be expected on a random basis.

Moreover, the meta-analysis authors used a fixed effects model, rather than the generally more valid random effects model to calculate the effects. Considering these and other statistical issues, prominent statisticians have reexamined the data considered in the meta-analysis, and more recent data, and concluded that "vitamin E intake is unlikely to affect mortality regardless of dose" (Berry et al. 2009).

In another meta-analysis example, the statistical procedures were apparently valid, but the inclusion/exclusion criteria were not presented in a logical fashion (Bjelakovic et al. 2007). In this meta-analyses of mortality in randomized trials, the researchers included beta-carotene, vitamin A, vitamin C, vitamin E, and selenium because they are all "antioxidants." This makes no more sense than including both glucose and cyanide data in the same meta-analysis because both are "carbon compounds." More specifically in this meta-analysis, selenium is known to decrease the risk of cancer in selenium-deficient high-risk groups in China, and beta-carotene is known to increase the risk of cancer in smokers and asbestos workers. Thus, including a known negative and known positive in a single meta-analysis should be expected to result in a null effect because the two effects cancel each other. This procedure amounts to erasing data that show meaningful effects. In this example, the statistical methods seem to have been acceptable but the inclusion/exclusion criteria were simply invalid.

A recent publication by the Cochrane Summaries (Bjelakovic et al. 2012) selected the same authors of the previously discussed meta-analysis (Bjelakovic et al. 2007) to perform an

"independent" review. The meta-analysis authors have a clearly established negative view of antioxidants, and it is mystifying how the Cochrane Summaries could consider their review to be independent. The Cochrane Summaries reached almost exactly the same conclusions as the previously cited meta-analysis (Bjelakovic et al. 2007). The selection of these reviewers raises concerns that the Cochrane managers had a viewpoint in advance of consideration of the scientific data.

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.

European Commission, Scientific Committee on Food (EC SCF 2003). The EC SCF 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.

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.

CRN Recommendations

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 synthetic *dl*-alpha-tocopheryl acetate (that is, *all rac*-alpha-tocopheryl acetate in the currently accepted scientific nomenclature), 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. CRN identifies a vitamin E UL of 1,600 IU from clinical trial data that showed no adverse effects at this level of intake (Gillilan et al. 1977). Correspondingly, 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 intake of 3,200 IU (Anderson and Reid 1974). With the conversion to mg alpha-TE as performed by the EVM, the CRN upper limit for supplements of 1,600 IU is equivalent to 1,073 mg, a value very similar to that identified by the IOM through extrapolation from animal data. The CRN upper limit for supplements applies to healthy adults who are not taking any anticoagulant drug.

Quantitative Summary for Vitamin E

CRN UL, supplemental intake	1,000 mg (1600 IU)/day
IOM UL, total intake	1,000 mg/day
EC SCF UL, total intake	300 mg/day
EC supplement maximum	Not determined
EVM SUL, supplemental intake	540 mg (800 IU)/day

References

Age-Related Eye Disease Study Research (AREDS) Group. 2001. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta-carotene, and zinc for age-related macular degeneration and vision loss: AREDS Report No. 8. *Arch Ophthalmol.* 19:1417–1436.

Anderson TW, Reid DBW. 1974. A double-blind trial of vitamin E in angina pectoris. *Am J Clin Nutr.* 27:1174–1178.

ATBC: The Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study Group. 1994. The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med.* 330:1029–1035.

Bendich A, Machlin LJ. 1988. Safety of oral intake of vitamin E. *Am J Clin Nutr*. 48:612–619.

Berry D, Walthen JK, Newell M. 2009. Bayseian model averaging in meta-analysis: vitamin E supplementation and mortality rate. *Clin Trials.* 6:28–41.

Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. 2007. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA.* 297:842–857.

Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. 2012. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Summaries. March 14, 2012. http://summaries.cochrane.org/CD007176/antioxidant-supplements-for-prevention-of-mortality-in-healthy-participants-and-patients-with-various-diseases#sthash.Sa1S6IG8.dpuf.

Brown BG, Zhao XQ, Chait A, et al. 2001. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med.* 345:1583–1592.

Cheung MC, Zhao XQ, Chait A, Albers JJ, Brown BG. 2001. Antioxidant supplements block the response of HDL to simvastatin-niacin therapy in patients with coronary artery disease and low HDL. *Arterioscler Thromb Vasc Biol.* 21:1320–1326.

Chylack LT Jr, Brown NP, Bron A, et al. 2002. The Roche European American Cataract Trial

(REACT): a randomized clinical trial to investigate the efficacy of an oral antioxidant micronutrient mixture to slow progression of age-related cataract. *Ophthalmic Epidemiol.* 9:49–80.

Corrigan JJ Jr. 1982. The effect of vitamin E on warfarin-induced vitamin K deficiency. *Ann NY Acad Sci*. 393:361-368.

Corrigan JJ Jr, Ulfers LL. 1981. Effect of vitamin E on prothrombin levels in warfarin-induced vitamin K deficiency. *Am J Clin Nutr.* 34:1701–1705.

Dickinson A. 2002. *The Benefits of Nutritional Supplements*. Washington, DC: Council for Responsible Nutrition.

Dolan Y, Lichtenberg D, Pinchuk I. 2009. No evidence supports vitamin E indiscriminate supplementation. *Biofactors.* 35:469–473.

Dowd P, Zheng ZB. 1995. On the mechanism of the anticlotting action of vitamin E quinone. *Proc Natl Acad Sci USA.* 92:8171–8175.

European Commission, Scientific Committee on Food (EC SCF). 2003. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin E. SCF/CS/NUT/UPPERLEV/31 Final Report. Brussels. http://ec.europa.eu/food/fs/sc/scf/out195_en.pdf.

Expert Group on Vitamins and Minerals (EVM), Committee on Toxicity. 2003. *Safe Upper Levels for Vitamins and Minerals*. London: Food Standards Agency Publications.

Gillilan RE, Mondell B, Warbasse JR. 1977. Quantitative evaluation of vitamin E in the treatment of angina pectoris. *Am Heart J*. 93:444–449.

Hemilä H, Kaprio J. 2011. Vitamin E may affect the life expectancy of men, depending on dietary vitamin C intake and smoking. *Age and Ageing*. 40:215–220.

Higdon J. 2004. Vitamin E web page. Linus Pauling Institute website. http://lpi.oregonstate.edu/infocenter/vitamins/vitaminE/. (Updated June 2008.)

HOPE Study Investigators. 2000. Vitamin E supplementation and cardiovascular events in high-risk patients. *N Engl J Med.* 342:154–160.

Institute of Medicine (IOM). 2000. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington, DC: National Academy Press.

Kappus H, Diplock AT. 1992. Tolerance and safety of vitamin E: a toxicological position report. *Free Radical Biology and Medicine*. 13:55–74.

Kim JM, White RH. 1996. Effect of vitamin E on the anticoagulant response to warfarin. *Am J Cardiol.* 77:545–546.

Knekt P, Aromaa A, Maatela J, et al. 1991. Vitamin E and cancer prevention. *Am J Clin Nutr.* 53:283S–286S.

Leppälä JM, Virtamo J, Fogelholm R, et al. 2000. Controlled trial of alpha-tocopherol and beta-carotene supplements on stroke incidence and mortality in male smokers. *Arterioscler Thromb Vasc Biol*. 20:230–235.

Meydani SN, Meydani M, Blumberg JB, et al. 1998. Assessment of the safety of supplementation with different amounts of vitamin E in healthy older adults. *Am J Clin Nutr*. 68:311–318.

Miller ER, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Gullar E. 2005. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern*

Med. 142:37–46.

Nelson, JS. 1980. Pathology of vitamin E deficiency. In: Machlin LJ, ed. *Vitamin E: A Comprehensive Treatise*. New York: Dekker; 397–428.

Parkinson Study Group. 1998. Mortality in DATATOP: a multicenter trial in Parkinson's disease. *Ann Neurol*. 43:318–325.

Rutkowski M, Grzegorczyk K. 2012. Adverse effects of antioxidative vitamins. *Int J Occup Med Environ Health*. 25:105–121.

Sies H, Stahl W. 1995. Vitamins E and C, B-carotene, and other carotenoids as antioxidants. *Am J Clin Nutr*. 62:1315S–1321S.

Sokol, RJ. 1996. Vitamin E. In: Ziegler EE, Filer, LJ, eds. *Present Knowledge in Nutrition.* 7th ed. Washington, DC: ILSI Press; 130–136.

Spencer AP. 2000. Vitamin E: cautionary issues. *Curr Treat Options Cardiovasc Med*. 2:1–3.

Stephens NG, Parsons A, Schofield PM, et al. 1996. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet.* 347:781–785.

Traber MG. 2006. Vitamin E. In: Shils ME, Shike M, Ross AC, Caballero B, Cousins R, eds. *Modern Nutrition in Health and Disease*. 10th ed. Baltimore: Lippincott Williams & Wilkins; 396–411.

Traber MG, Manor D. 2012. Vitamin E. *Adv Nutr*. 3:330–331.

Waters DD, Alderman EL, Hsia J, et al. 2002. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. *JAMA*. 288:2432–2440.