Vitamins E and C are safe across a broad range of intakes[1,2]

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ABSTRACT

A robust database shows that dietary supplements of vitamins E and C are safe for the general population. Because these nutrients supply antioxidant and other functions for homeostasis and protection against free radical damage, supplementation has been intensively studied. Because of perceived benefits, many persons consume quantities of vitamins E and C well above the recommended dietary allowances. As safety guidance, tolerable upper intake levels have been established by the Food and Nutrition Board, Institute of Medicine, at 1000 mg for vitamin E and 2000 mg for vitamin C in adults. Many clinical trials with these vitamins have involved subjects with various diseases, and no consistent pattern of adverse effects has occurred at any intake. Numerous studies of vitamin C supplementation have provided no pattern of evidence to support concerns about safety other than occasional gastrointestinal upset or mild diarrhea resulting from the osmotic effects of unabsorbed quantities of vitamin C. Evidence of bleeding effects and other potential adverse effects of high vitamin E intakes in humans is not convincing. Evidence of adverse effects of vitamin C that result from its effects on iron absorption and metabolism has not been confirmed in clinical trials. Thus, we conclude from clinical trial evidence that vitamin E supplements appear safe for most adults in amounts ≤1600 IU (1073 mg *RRR*-α-tocopherol or the molar equivalent of its esters) and that vitamin C supplements of ≤2000 mg/d are safe for most adults. *Am J Clin Nutr* 2005;81:736–45.

KEY WORDS Vitamin E, α-tocopherol, tocopherol, vitamin C, ascorbic acid, risk assessment, safety, clinical trials

INTRODUCTION

In the Western world, intakes of vitamins E and C are rarely low enough to cause overt deficiency diseases. Low intakes of these antioxidant micronutrients may, however, increase the risk of certain chronic diseases and accelerate several indicators of the aging process. These effects may be at least partly due to inadequate protection of tissues against oxidative damage from free radicals. Numerous studies suggest that supplements of vitamin E, vitamin C, or both may contribute, in many situations, to lowering the risk of specific chronic diseases such as Alzheimer disease, age-related macular degeneration, some types of cancer, cataracts, and ischemic heart disease (IHD). Because of much supporting evidence, the hypothesis that antioxidant activity may help decrease the risk of these diseases is viable, despite the fact that several clinical trials failed to find benefit (1–9). It is estimated that ≈70% of the US population uses dietary supplements at least occasionally, and ≈40% uses supplements on a regular basis (10, 11). The most commonly used supplements are multivitamins, vitamin C, vitamin E, and calcium.

DIETARY REFERENCE INTAKES FOR VITAMINS E AND C

The Food and Nutrition Board (FNB) of the Institute of Medicine, a part of the US National Academies, has established a system of dietary reference intake (DRI) values for the US population that, for the first time, provides advice on the safety of the nutrients. "Safety" is defined as presenting no "unreasonable risk of illness or injury" or "a reasonable certainty of no harm," under labeled or ordinary conditions of use, as set forth in US laws and regulations for dietary supplements and food additives. The DRI system includes the estimated average requirement, the recommended dietary allowance (RDA) [or the acceptable intake for some nutrients], and the tolerable upper intake level (UL) (12). The RDA (or acceptable intake) represents the recommended daily intake for meeting normal nutritional needs and preventing clinical deficiency. Compared with the previous RDA, the new recommendations for vitamin E have been increased by ≈50% for men and by almost 100% for women. Similarly, the new recommendations for vitamin C have been increased by 25% for women and by 50% for men. The DRI values include a UL, which is the maximum amount considered safe (ie, likely to pose no risk) for healthy people when used daily for long periods. The RDA and UL values are based on exhaustive reviews of the scientific literature. RDA and UL values for vitamins E and C are shown in **Table 1**.

Authoritative safety evaluations, including those by the FNB, the European Commission's Scientific Committee for Food (13)

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TABLE 1
Recommended dietary allowance (RDA) and tolerable upper intake levels (UL) for vitamins E and C[1]

	Vitamin E (α-tocopherol equivalents)[2]	Vitamin C (ascorbic acid)
	mg	
RDA		
Men	15	90[3]
Women	15	75[3]
UL	1000	2000

[1] Food and Nutrition Board (12). UL, the highest level of regular daily intake that is likely to pose no risk of adverse health effects to almost all persons in the general population; RDA, the amount considered to maintain normal nutrition in the general population.

[2] The new recommendations for vitamin E are expressed as milligrams of *RRR*-α-tocopherol equivalents. Dietary supplements of vitamin E are labeled in terms of international units (IU). One mg of synthetic vitamin E (*all-rac*-α-tocopheryl acetate is equivalent to 1 IU vitamin E, but only 0.45 mg *RRR*-α-tocopherol. One mg of natural vitamin E (*RRR*-α-tocopherol) provides 1.5 IU. For the UL, the Food and Nutrition Board recommended 1000 mg of any α-tocopherol form, which is equivalent to 1500 IU *RRR*-or 100 IU *all-rac*-α-tocopherol.

[3] Increase by 35 mg for smokers.

or its European Food Safety Authority (14) and the United Kingdom's Expert Group on Vitamins and Minerals (EVM; 15), have addressed the safety of vitamins C and E separately under the assumption that there will be little or no interaction of toxicologic importance.

VITAMIN E: THE EVIDENCE FOR SAFETY

Several frequently cited literature reviews meticulously document the very consistent absence of adverse effects of vitamin E at intakes well above the RDA (16). The cited research included randomized, double-blind, placebo-controlled trials with large patient populations. Kappus and Diplock (17) similarly observed that many such scientifically reliable studies consistently showed no important adverse effects associated with vitamin E supplementation at intakes ranging up to 3200 IU/d. A recent meta-analysis that combined the results of 19 clinical trials of vitamin E supplementation for various diseases, including heart disease, end-stage renal failure, and Alzheimer disease, reported that adults who took supplements of ≥400 IU/d were 6% more likely to die of any cause than those who did not take vitamin E supplements (18). However, further breakdown of the risk by vitamin E dose and adjustment for other vitamin and mineral supplements found that the increased risk of death was significant only at a dose of 2000 IU/d, which is higher than the UL for adults. Furthermore, 3 other meta-analyses that combined the results of randomized controlled trials designed to evaluate the efficacy of vitamin E supplementation for the prevention or treatment of cardiovascular disease (CVD) found no evidence that vitamin E supplementation up to 800 IU/d significantly increased or decreased CVD mortality or all-cause mortality (19–21). At present, the evidence is not convincing that vitamin E supplementation up to the UL increases the risk of death due to CVD or other causes.

Few reports have cited any adverse effects of long-term use of vitamin E supplements at intakes up to many times the RDA. The evidence comes from many types of studies, ranging from observational studies of a few subjects to large, randomized, controlled intervention trials designed to ascertain whether there are beneficial effects on cancer, CVD, or other disorders. More than 20 published clinical trials involving ≥80 000 subjects have documented the safety of vitamin E supplements, as highlighted in **Table 2**.

In a double-blind crossover study by Gillilan et al (22), 48 patients with stable angina documented by electrocardiography and angiography were randomly assigned to receive 1600 IU vitamin E/d for 6 mo either before or after a 2-mo placebo period. Although vitamin E did not appear to improve symptoms or exercise capacity in these patients with well-established heart disease, it proved entirely safe for them at that dose. There were no significant differences in symptomatic or laboratory indexes of heart disease in these patients between the active therapy and placebo periods.

Meydani et al (23) conducted an extensive 4-mo safety study of vitamin E (*all-rac*-α-tocopherol) at 60, 200, or 800 IU/d in 88 healthy elderly persons. None of the subjects reported any side effects. None showed any abnormalities on a wide array of laboratory tests, which included plasma proteins and lipids; glucose; lipoproteins, bilirubin, and other variables of liver, kidney, and metabolic function; red blood cell counts; bleeding time and other variables of coagulation; and a wide range of immune function indicators.

These findings from 2 small trials were corroborated by the larger Cambridge Heart Antioxidant Study, in which 2002 patients with symptomatic and angiographic CVD were randomly assigned to receive placebo or vitamin E at 400 or 800 IU/d (24). Over a median follow-up of 510 d, no significant adverse effects of vitamin E supplementation were reported among these patients. The slight numerical excesses of fatal myocardial infarction and total deaths with vitamin E treatment were not statistically significant. The rate of treatment discontinuation due to adverse effects—a common gauge of patient tolerance—was only 0.55% for the entire population and did not differ significantly between actively treated and control patients.

The Heart Outcomes Prevention Evaluation Study was an evaluation of the angiotensin-converting enzyme inhibitor ramipril, vitamin E given at 400 IU/d, or both in 9541 patients with multiple CVD risk factors (5). The Heart Outcomes Prevention Evaluation Study investigators concluded that vitamin E was "well tolerated" because the number of adverse events with the treatment was not significantly greater than that with the placebo over the mean follow-up of 4.5 y.

Chylack et al (6), Brown et al (35), and Cheung et al (39) tested the combination of simvastatin and niacin, with or without an antioxidant cocktail containing 800 IU vitamin E/d, against the cocktail alone or matching placebos in 160 patients with clinical IHD, low concentrations of HDL cholesterol, and healthy concentrations of 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 with the drug treatments (39). The DATATOP clinical trial of 800 subjects for 8.2 y found no adverse effects of 2000 IU vitamin E/d (31). The data from this study support the safety of very high intakes of vitamin E over a long period.

The α-Tocopherol, β-Carotene Cancer Prevention Study (ATBC Study) raised a flag of caution (2). Among 29 133 male

TABLE 2
Published safety observations for vitamin E supplementation[1]

Study and population	Features	Dosage and study design	Duration	Safety observations[2]
Anderson and Reid (25) $n = 36$	Symptomatic ischemic heart disease	3200 IU/d; randomized, controlled	9 wk	No significant subjective or objective adverse effects
Farrell and Bieri (26) $n = 28$	Volunteers	100–800 mg/d; observational	2.9 y[3]	No safety concerns by clinical and laboratory criteria
Gillilan et al (22) $n = 48$	Symptomatic ischemic heart disease	1600 IU/d; double-blind, crossover	6 mo plus 6 mo	No subjective adverse effects; no adverse clinical or laboratory findings
Inagaki et al (27) $n = 75$	Heart disease	200 mg/d; randomized, controlled	4–6 wk	No significant adverse effects
Stampfer et al (28) $n = 30$	Volunteers	800 IU/d; randomized, controlled	16 wk	No reported adverse effects
Bierenbaum et al (29) $n = 25$	Diabetes	2000 IU/d; randomized, controlled	6 wk	No subjective adverse effects; no adverse clinical or laboratory findings
ATBC Cancer Prevention Study (2, 3) $n = 29\,133$	Male smokers aged 50–69 y	50 mg/d; randomized, controlled	5–8 y	Vitamin E was associated with somewhat higher incidence of hemorrhagic stroke and lower incidence of ischemic stroke than was placebo, which created a lower but nonsignificant decrease in overall stroke risk
Stephens et al (CHAOS trial) (24) $n = 2002$	Symptomatic ischemic heart disease	400 or 800 IU/d; randomized, controlled	510 d[4]	Only 0.55% of patients discontinued treatment because of adverse effects (no difference between active and control groups)
Sano et al (30) $n = 341$	Alzheimer patients (moderate)	2000 IU/d; randomized, controlled	2 y	No significant differences among the groups in adverse-event categories after adjustment for multiple comparisons
Meydani et al (23) $n = 88$	Volunteers	60–800 IU/d; randomized, controlled	4 mo	No subjective adverse effects; no adverse clinical or laboratory findings
Parkinson study group (31) $n = 800$	Patients with Parkinson disease	2000 IU/d; randomized, controlled	8.2 y	No adverse effects reported
GISSI Investigators (4) $n = 11\,324$	Recent heart attack	300 mg/d; randomized, controlled	3.5 y[3]	No adverse effects reported
HOPE Study Investigators (5) $n = 9541$	Multiple CVD risk factors	400 IU/d; randomized, controlled	4.5 y[3]	No significant adverse effects
Boaz et al (SPACE trial) (32) $n = 196$	CVD patients on hemodialysis	800 mg/d; randomized, controlled	519 d[4]	No adverse effects reported
Salonen et al (ASAP study) (33) $n = 520$	Smokers and nonsmokers; men and postmenopausal women	91 mg/d; randomized, controlled	3 y	No significant adverse effects
AREDS Research Group (34) $n = 3640$	Age-related macular degeneration and vision loss	400 IU/d; randomized, controlled	6.3 y[3]	Antioxidant cocktail significantly associated with increases in rate of skin yellowing
Brown et al (35) $n = 160$	Clinical CVD; low HDL; normal LDL	800 IU/d; randomized, controlled	3 y	No reported clinical adverse effects due to antioxidant vitamins; antioxidant cocktail blunted the HDL-elevating effect of combined simvastatin-niacin
Lonn et al (SECURE trial) (7) $n = 732$	Vascular disease or diabetes	400 IU/d; randomized, controlled	4.5 y[3]	No significant adverse effects
de Gaetano (PPP study) (36) $n = 4495$	CVD risk factors	300 mg/d; randomized, controlled	3.6 y[3]	No adverse effects reported
Chylack et al (REACT study) (6) $n = 297$	Outpatients with cataracts	600 mg/d; randomized, controlled	2–4 y	No safety concerns
Hodis et al (VEAPS study) (8) $n = 332$	Hypercholesterolemia but no CVD	400 IU/d; randomized, controlled	3 y[3]	No significant adverse effects
Taylor et al (VECAT study) (37) $n = 1193$	Healthy elderly subjects	500 IU/d; randomized, controlled	4 y	No significant adverse effects
HPS Collaborative Group (9) $n = 20\,536$	Vascular disease; diabetes	600 mg/d; randomized, controlled	5 y	No safety concerns
Salonen et al (ASAP study) (38) $n = 520$	Smokers and nonsmokers; men and postmenopausal women	272 IU vitamin E/d and 500 mg vitamin C/d; randomized, controlled	6 y	No safety concerns suggested; benefit of reduced atherosclerotic progression

[1] ATBC, α-Tocopherol, β-Carotene Cancer Prevention; CHAOS, Cambridge Heart Antioxidant Study; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico; HOPE, Heart Outcomes Prevention Evaluation; SPACE, Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease; ASAP, Antioxidant Supplementation in Atherosclerosis Prevention; AREDS, Age-Related Eye Disease Study; SECURE, The Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E; PPP, Primary Prevention Project; REACT, Roche European American Cataract Trial; VEAPS, Vitamin E Atherosclerosis Prevention Study; VECAT, Vitamin E, Cataract, and Age-related Maculopathy Study.
[2] Terms used are characterizing but not verbatim descriptions from cited sources.
[3] $\bar{x}$.
[4] Median.

smokers in Finland, aged 50–69 y, supplementation with vitamin E at 50 mg/d (*all-rac*-α-tocopheryl acetate, and therefore 50 IU/d) for 5–8 y was associated with a 7.8% rate of death due to hemorrhagic stroke and with a 5.2% rate among those receiving placebo (66 cases in the vitamin group and 44 in the control group). In contrast, the vitamin E group had a significantly lower incidence of prostate cancer and significantly lower mortality due to ischemic stroke than did the placebo group. Ischemic stroke is more frequent than hemorrhagic stroke, and the overall stroke rate was lower in the vitamin E group than in the placebo group. However, statistical significance was not indicated for any of these apparent differences. The authors concluded only that the observation of higher hemorrhagic stroke mortality with vitamin E than with placebo required careful review. In a further evaluation, the researchers concluded that α-tocopherol supplementation increased the risk of fatal hemorrhagic strokes but prevented cerebral infarction (3). In that study, there were, within 3 mo of the initial stroke diagnosis, 85 deaths due to subarachnoid hemorrhagic stroke; the number of such deaths in the vitamin E–supplemented group increased by 50%, for a total of 28 more deaths than in the placebo group. In contrast, there were 807 deaths due to cerebral infarction; the number of such deaths in the vitamin E–supplemented group decreased by 14%, for a total of 53 fewer deaths than in the placebo group. The overall net effects of vitamin E on the incidence of and mortality from total strokes were not significant.

A few reports other than the ATBC Study have suggested that bleeding complications may be associated with vitamin E supplementation. High intake of vitamin E can influence coagulation in some persons with drug-induced vitamin K deficiency, but most evidence suggests this effect does not occur in persons with adequate amounts of vitamin K, who represent well over half of the population (40–42). Moreover, a large trial of patients taking long-term warfarin who also took 800–1200 mg vitamin E/d showed no changes in coagulation variables that would suggest an increased risk of bleeding (43). A small clinical trial indicated that proteins induced by vitamin K absence–factor II, an accepted indicator of poor vitamin K status, increased with daily administration of 1000 IU *RRR*-α-tocopherol, but the clinical significance of this finding, if any, is not clear (44). Vitamin E may also affect coagulation through its actions on platelets. In addition, high vitamin E intakes inhibit protein kinase C and consequently limit the ability of platelets to clot (45). The platelet effects of vitamin E may produce health benefits.

Even the hemorrhagic-stroke mortality findings of the ATBC Study have not altered the prevailing consensus that vitamin E intake up to UL is safe, partly because that effect has not been seen in other trials using higher dosages and partly because the overall stroke risk was decreased. The Institute of Medicine report that delineated the DRI values for vitamins E and C stated that the "preliminary" ATBC Study findings were "not convincing" in the absence of corroboration in other large-scale clinical trials (12).

VITAMIN C: THE EVIDENCE FOR SAFETY

The preponderance of scientific evidence, which has been thoroughly reviewed by several authors, shows consistently that vitamin C is safe at intakes of ≤2000 mg/d (1, 9, 46, 47). Several hypothesized adverse effects—including the hypotheses of adverse effects of increased oxalate and kidney stone formation, increased uric acid concentrations, excess iron absorption, reduced vitamin B-12 concentrations, systemic conditioning (induced scurvy), and prooxidant effects—were examined in detail and were found to have no substantive basis (12).

Although vitamin C supplementation may be less studied than vitamin E supplementation for the prevention for chronic disease, several clinical trials are relevant to its safety evaluation (**Table 3**). For example, in the Roche European American Cataract Trial (6), the Age-Related Eye Disease Study (34), and the simvastatin-niacin study of Brown et al (35), patients who received the vitamin cocktails also ingested vitamin C at doses of 750, 500, and 1000 mg/d, respectively. A combination of 800 IU vitamin E/d and 1000 mg vitamin C/d has been reported to attenuate the beneficial effects of a combined simivastatin-niacin treatment when measured as angiographic endpoints, but it had no significant effects on the treatment's clinical endpoints (6). The meaning of this observation with respect to the safety of vitamin E, vitamin C, or both in the presence or absence of simivastatin and niacin is not known.

In the Medical Research Council and British Heart Foundation Heart Protection Study, 20 536 adults in the United Kingdom with IHD or other occlusive vascular disease or diabetes were randomly assigned to receive 250 mg vitamin C/d (along with vitamin E and β-carotene) or placebo for 5 y (9). In this controlled trial with an unusually long follow-up, no clinically important safety issues arose.

Because vitamin C assists in the absorption of dietary iron, some research has focused on whether increased vitamin C intake inopportunely increases iron stores. The literature in general suggests that iron absorption does increase with rising vitamin C intake, especially at vitamin C intakes of 25 to 50 mg/d. Above that intake, vitamin C has little effect on iron uptake. Most published studies on the subject strongly indicate that vitamin C supplement doses up to 2000 mg/d do not increase body iron stores enough to produce any clinically significant adverse effects (9, 76). Cook et al (77) studied iron absorption in 17 healthy volunteers who received vitamin C at 2000 mg/d at meals for 16 wk; 9 subjects continued taking it for a total of 24 mo. Iron stores and effects were not enhanced by 2000 mg vitamin C/d, and subjects reported no instances of gastrointestinal upset or any other significant side effect.

Other evidence contradicts the few reports of adverse effects other than mild osmotic diarrhea associated with vitamin C supplementation, and collectively the other hypothesized adverse effects are of undetermined relevance (30, 78–80). Intakes of vitamin C well in excess of 2000 mg/d have sometimes been associated with gastrointestinal upset or skin rashes, but other evidence suggests that intakes up to 4000 mg/d are well tolerated in the general population.

Some case reports suggest that unusually high intakes of vitamin C, especially in persons who are given the vitamin intravenously or who have chronic renal failure, may be associated with the development of oxalate kidney stones (81). However, it is uncertain whether this risk occurs in the general population (78). An epidemiologic study found that the risk of kidney stones is significantly lower in men who consume ≥1500 mg vitamin C/d than in those who consume <250 mg vitamin C/d (82). Much evidence indicates that the "finding" of increased oxalate excretion in persons with high intakes of vitamin C actually is an analytic artifact resulting from a method that converts vitamin C in the test sample to oxalate during the analysis of the urine (83).

TABLE 3
Published safety observations for vitamin C supplementation[1]

Published study and population	Features	Dosage and design	Duration	Safety observations[2]
Stein et al (48) $n = 3$	Volunteers	8 g/d, divided dose; observational	3–9 d	Urinary uric acid increased 41–51%, resulting in uricosuria in 1 volunteer
$n = 9$	Hyperuricemia patients	4 g, single dose; controlled	2 h	Uric acid and creatinine clearance increased 202%; mild diarrhea noted in 1 patient
Creagan et al (50) $n = 150$	Advanced cancer patients	10 g/d, divided dose; randomized, controlled	≈50–210 d	No significant differences in reported side effects by group
Ludvigsson et al (51) $n = 24$	Volunteers	1000–4000 mg/d; randomized, controlled	28 d	No clinical or biochemical adverse effects noted
Knodell et al (52) $n = 175$	Cardiac patients	3200 mg/d; randomized, controlled	16 d	No clinical adverse effects noted
Tsao and Salimi (53) $n = 6$	Volunteers	10 g/d, divided dose; observational	12–20 d	Urinary oxalate increased 16% but remained in reference range
Moertel et al (54) $n = 100$	Advanced colorectal cancer patients	10 g/d; randomized, controlled	≈7–126 d	No significant differences in reported side effects by group
Ono (55) $n = 59$	Renal failure patients	500 mg/d; controlled	28 d	Aggravation of hyperoxalemia (+118%)
Omaye et al (56) $n = 11$	Volunteers	600 mg/d; metabolic trial (depletion-supplementation-depletion design)	92 d	Accelerated plasma losses of vitamin C or purponted conditioned deficiency noted after second depletion period
Brigden et al (57) $n = 5$	Volunteers	100–1000 mg/d; observational	7 d	Fivefold increase in incidence of false-negative for hemoglobin and glucose by using dipstick urinalysis
Johnston et al (58) $n = 9$	Volunteers	500–2000 mg/d	28 d	Diarrhea reported in 3 subjects and nosebleeds in 2 subjects
Hunt et al (59) $n = 25$	Volunteers	1500 mg/d, divided dose; randomized, controlled	35 d	No effect on biochemical indexes of iron status
Wandzilak et al (60) $n = 15$	Volunteers	1–10 g/d, divided dose; observational	5 d	Urinary oxalate increased 18–40% but remained in reference range
Fuller et al (61) $n = 19$	Smokers (≥5 pack-years)	1000 mg/d, divided dose; randomized, controlled	28 d	No adverse biochemical effects noted
Jacob et al (62) $n = 20$	Volunteers	500 mg/d; controlled	42 d	No adverse biochemical effects noted
Levine et al (49) $n = 7$	Volunteers	30–2500 mg/d, divided dose; controlled metabolic study	≈40 d	Urinary oxalate increased 0–40% but remained in reference range; urinary uric acid increased 0–20% (above reference range); no clinical adverse effects noted
Podmore et al (63) $n = 30$	Volunteers	500 mg/d; controlled	42 d	No effect on total white cell oxidative DNA damage
Rehman et al (64) $n = 20$	Volunteers (high plasma vitamin C: 72 ± 14 μmol/L)	60 or 260 mg/d taken with iron supplement (14 mg/d); randomized, controlled	84 d	Transient rise in total white cell oxidative DNA damage (42 d), which reverted to baseline with continued supplementation (84 d)
Fuller et al (65) $n = 30$	Smokers (>10 cigarettes/d)	1000 mg/d; randomized, controlled	56 d	No clinical or biochemical adverse effects noted
Vojdani et al (66) $n = 20$	Volunteers	500–5000 mg/d; randomized, controlled	14 d	No biochemical adverse effects noted
Brennan et al (67) $n = 14$	Volunteers	500 mg/d, divided dose; randomized, controlled	42 d	No biochemical adverse effects noted
Porkkala-Saratoho et al (ASAP study) (68) $n = 520$	Volunteers	500 mg/d, divided dose	3 y	No reported adverse effects
Levine et al (69) $n = 15$	Volunteers	30–2500 mg/d, divided dose; controlled metabolic study	≈45 d	No clinical adverse effects noted
Johnston and Cox (70) $n = 10$	Volunteers	75–2000 mg/d; controlled	70 d	Diarrhea reported in 1 subject

(*Continued*)

TABLE 3 (*Continued*)

Published study and population	Features	Dosage and design	Duration	Safety observations[2]
AREDS Study Research Group (34) $n = 3640$	Age-related macular degeneration patients	500 mg/d (combined with vitamin E and β-carotene); randomized, controlled	<6 y	No significant serious adverse effects noted
MRC/BHF Heart Protection Study (9) $n = 20\,536$	Ischemic heart disease patients	250 mg/d (combined with vitamin E and β-carotene)	5 y	No significant serious adverse effects noted
Hajjar et al (71) $n = 54$	Volunteers	500–2000 mg/d, divided dose	8 mo	No clinical intolerance or adverse effects noted
Huang et al (72) $n = 184$	Volunteers	500 mg/d; randomized, controlled	56 d	No adverse effects reported
Aghdassi et al (73) $n = 57$	Crohn disease patients	1000 mg/d (combined with vitamin E); randomized, controlled	28 d	No significant difference in clinical adverse effects noted
Lenton et al (74) $n = 48$	Volunteers (plasma vitamin C < 33 μmol/L)	500–1000 mg/d; controlled	91 d	No adverse effects reported

[1] ASAP, Antioxidant Supplementation in Atherosclerosis Prevention; AREDS, Age-Related Eye Disease Study; MRC/BHF, Medical Research Centre/British Heart Foundation.

[2] Terms used are characterizing but not verbatim descriptions from cited sources.

Hoffer (84) commented, "[T]he idea that ingestion of ascorbic acid in large doses causes kidney stones has become established...[and] by constant repetition this idea, based entirely on conjecture, has become enshrined as fact." Fortunately, the authoritative opinion of the FNB (12) has begun to replace the widely accepted misconception that vitamin C causes kidney stones. One study of young adults found an increase in oxalate excretion that remained in the normal range (48). No clinical significance of this observation has been established.

Increased uric acid concentrations have been observed in a few studies (12, 48, 49), but no increases were found in other studies that measured the plasma or urinary concentrations (or both) of uric acid (85–87). The health effects of the moderate increase in uric acid observed in a few studies but not in others are unknown (88) and are not an appropriate basis for a safety evaluation through risk assessment (12).

With respect to the new reference intakes for vitamin C, Frei and Traber (89) commented, "[T]here [are] currently no consistent and compelling data for serious adverse health effects of vitamin C in humans, and a UL, therefore, cannot be established." Nonetheless, the Institute of Medicine considered the mild and transient diarrhea that can result from high intakes of vitamin C to fit the definition of a "hazard" under the protocol of the UL method, and it used related data to set a UL of 2000 mg/d.

An epidemiologic analysis of vitamin C intake found a correlation with increased risk of CVD mortality in postmenopausal women with diabetes (90). Vitamin C intake, including that from supplements, was unrelated to mortality due to CVD in subjects who were nondiabetic at baseline, and therefore the main findings apparently have no implications for healthy adults.

COMBINATIONS OF VITAMINS E AND C: THE EVIDENCE FOR SAFETY

Several large or long-term clinical trials have employed combinations of vitamins E and C, sometimes with additional agents, as already discussed. For example, the combination of vitamins E and C used in the Antioxidant Supplementation in Atherosclerosis Prevention Study, the Roche European American Cataract Trial, the Age-Related Eye Disease Study, and the Medical Research Centre/British Heart Foundation trials, as well as the simvastatin-niacin study of Brown et al were already described for their antioxidant treatments (6, 34, 35, 38, 91). These studies support the safety of vitamin E and C in combination.

The data from the Women's Angiographic Vitamin and Estrogen Trial of 423 postmenopausal women treated with a combination of vitamins C and E, hormone replacement therapy, or both were interpreted by the authors as showing potential adverse effects from the combined supplement of 400 IU vitamin E and 500 mg vitamin C given twice daily (for totals of 800 IU and 1000 mg, respectively; 92). The design and execution of this trial, however, prevent any such conclusion; the trial focused on clinical endpoints that were beyond the statistical power of the study to detect. The methods exaggerated the potential adverse effects by assigning worst-case values to angiographic values when the values could not be obtained, and it did not correct for multiple comparisons, thereby biasing the results against the safety of the vitamins (93). Therefore, the Women's Angiographic Vitamin and Estrogen Trial does not contradict the conclusion that vitamins E and C, or their combination, are safe at these or higher intakes.

A recent meta-analysis concluded that there is no evidence that antioxidant supplements prevent gastrointestinal cancers but, instead, seem to increase overall mortality (94). The purpose of a meta-analysis is to apply statistical procedures that integrate the results of several independent studies considered to be "combinable," thereby increasing the statistical power (95). Thus, the clinical trials of selenium should not be combined with those of β-carotene and vitamin E. Selenium trials have shown significant reductions in several, but not all, types of cancer. Two of the trials that included β-carotene found significant increases in mortality that were linked to increases in lung cancer risk in populations of long-term heavy smokers, asbestos workers, or both. These 2 trials almost exclusively biased the meta-analysis toward unfavorable results, but only when the fixed-effects model rather than the more appropriate random-effects meta-analysis was applied. In contrast to the restricted fixed-effects analysis, the most

highly aggregated meta-analysis showed a nonsignificant protective effect (relative risk: 0.96) when all trials, all treatments, and all types of cancer observed were considered.

MAXIMUM SAFE INTAKES OF VITAMINS E AND C

The UL is defined by the FNB (96) as the highest daily nutrient intake that is likely to pose no risk of adverse health effects to almost all persons in the general population. The UL method is an adaptation of a general method in quantitative toxicology. It is similar to but has important differences from the acceptable daily intake method that is widely used to set regulatory limits for food additives and pesticide residues in foods. Both the UL and the acceptable daily intake involve identification of an intake that is a no-adverse-effect level (NOAEL) or a lowest-adverse-effect level (LOAEL), evaluation of uncertainty, and calculation of an intake that is expected to carry no significant risk of adverse effects, ie, the UL or acceptable daily intake. The UL and acceptable daily intake methods differ markedly in the way they address uncertainty. The UL method uses uncertainty factors (UFs) that are fully derived from the specific database for each substance under consideration. For derivation of a UL from human data, the FNB has utilized UFs that range from 1 to 5, with values of 1.5 to 2 being most common. When deriving the UL from animal data, higher uncertainty factors are used to account for the uncertainties in extrapolation between species.

The NOAEL (or LOAEL) data are selected on the basis of considerations of evidence of causality, relevance, and the quality and completeness of the database. The UL is calculated as

$$\text{UL} = \text{NOAEL (or LOAEL)} \div \text{UF} \qquad (1)$$

Vitamin E

For vitamin E, the FNB did not find credible and reliable evidence of adverse effects in humans, and thus it decided to extrapolate from experimental animal data (4). Because no NOAEL could be identified, the LOAEL was used as the basis for calculating the UL, as follows: LOAEL = 500 mg $\cdot$ kg^{-1} $\cdot$ d^{-1}, and, for the UFs, LOAEL-to-NOAEL conversion = 2; subchronic to chronic exposure = 2; animals to humans = 3; and the composite UF = 36.

$$\text{UL} = 500 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1} \div 36 \times 68.5 \text{ kg body wt for adults} = 1000 \text{ mg (after rounding)} \qquad (2)$$

The FNB assigned the same UL (in mg) to all forms of vitamin E, regardless of the nutritional activity of each form. By using the same overall database, the EVM identified a UL of 800 IU (actually a NOAEL range of 800 to 1600 IU) from human clinical trial data obtained with 800 IU *all-rac*-α-tocopherol (23) and 1600 IU *all-rac*-α-tocopheryl acetate (22)—a UL that was supported by the results obtained with 800 IU in the Cambridge Heart Antioxidant Study (24)—and calculated the number of *RRR*-α-tocopherol equivalents (15). In addition, on the basis of the size and robustness of the human database, an uncertainty factor of 1 was assigned. Thus, the EVM approach implies different ULs for the different chemical forms of vitamin E. The Scientific Committee for Food set the vitamin E UL at 300 mg (13) on the basis of the data of Meydani et al (23) from a clinical trial that included amounts up to 800 IU/d. The Scientific Committee for Food provided no specific justification for its de facto discounting of all other data from other human studies at higher intakes—studies that also found no adverse effects.

In the absence of compelling data, regulators and policy advisors must decide whether to convert from IU to mg. If the UL or other safety level is derived from data related to one of the less active forms of vitamin E, conversion of IU to mg will further restrict the use of the more active forms, perhaps unnecessarily so. If the UL is derived from a very active form of vitamin E, conversion will result in a larger permissible intake of the less active forms.

On the basis of the totality of human evidence, we identified a vitamin E UL of 1600 IU/d, and we recommend the use of standard molecular weight–conversion factors to calculate the weight equivalents for the different chemical forms. Thus, the corresponding UL value for *RRR*-α-tocopherol would be 1070 mg. Intakes of vitamin E from conventional foods are smaller than this UL, and thus 1600 IU/d represents a supplemental intake that is safe for the general population. In the absence of compelling data, the conversion for safety assessment from IU to mg is a reasonable decision. Our evaluation of vitamin E safety differs from that of the FNB in that our safety level is derived only from human clinical trial data, whereas the FNB's UL is calculated from animal data. Numerically, the 2 values are similar.

Vitamin C

The FNB could not identify a NOAEL for vitamin C, but it did identify a LOAEL of 3000 mg/d, on the basis of data related to osmotic diarrhea and other gastrointestinal disturbances (12). Consideration of the transient and relative mildness of these effects contributed to the selection of a UF of 1.5. Thus, for most adults, the vitamin C UL is:

$$\text{UL} = 3000 \text{ mg/d} \div 1.5 = 2000 \text{ mg/d} \qquad (3)$$

The FNB considered but did not find credible or convincing several other often-claimed adverse effects of vitamin C, including increased oxalate formation, increased uric acid excretion, excess iron absorption, reduced vitamin B-12 concentrations, systemic conditioning, and prooxidant effects. On the basis of human studies of the osmotic diarrhea that can result from large bolus ingestions of vitamin C, we recommend a UL of 2000 mg/d for supplemental vitamin C. The gastrointestinal effects do not have a sharp dose-response threshold and do not represent severe or persistent effects; thus, they allow a relatively narrow margin of safety (representing a small UF) between the LOAEL and the UL. The UL does not apply to potential adverse effects for sensitive subpopulations, such as (possibly) homozygotes or even heterozygotes for hemochromatosis.

The EVM review agreed with the FNB that the LOAEL for vitamin C (based on the potential for gastrointestinal irritation, osmotic diarrhea, or both) is 3000 mg/d. The EVM selected an uncertainty factor of 3, even though it acknowledged that the effects are mild and infrequent, and thereby it calculated a guidance concentration of 1000 mg/d. The European Food Safety Authority recently published a safety evaluation for vitamin C but specified 1000 mg as a "guidance" rather than a more definitive UL (14).

The ULs for vitamin C and E (and all other nutrients) are set independently and with the assumption in each case that other

nutrient intakes are not elevated, or, if they are elevated, that high intakes of the others do not change the UL for the nutrient under consideration. There has been no broad-based systematic research to ascertain whether high intakes of one nutrient could potentiate the adverse effects of another. The adverse effect of vitamin C (osmotic diarrhea) is not known to be influenced by vitamin E, and the adverse effect of vitamin E (hemorrhagic potential) is not known to be influenced by vitamin C. Thus, there is no mechanistic rationale by which to hypothesize that either of these vitamins would influence the UL for the other. Because vitamin C and vitamin E are often consumed in quantities close to the UL, the history of use without obvious adverse interactions also suggests that a high intake of one of the vitamins does not significantly increase the potential for adverse effects of the other.

CONCLUSIONS

Vitamin E and C dietary supplements are used widely in the United States and other industrialized countries. The fact that adverse effects are rarely reported for vitamins E and C at amounts higher than the RDA is testimony to the safety of such dietary supplementation up to the UL. Several literature reviews have concluded, on the basis of a survey of published evidence, that such intake does not cause adverse side effects or create other safety issues. The definitive FNB report on recommended RDA and UL values states that the upper limits were designed "to protect the most sensitive individuals in the general population." The UL is not intended to apply to the most sensitive persons in sensitive subpopulations, such as those with phenylketonuria or Wilson's disease but, instead, to apply to the healthy general population, including its normal range of variation. The recommendations are entirely based on the available scientific evidence; the main caveat is that healthy persons should not "routinely" take the vitamins in amounts higher than the UL. Beyond that, the recommendations support the consensus of published studies that vitamin E doses up to 1000 mg/d and vitamin C doses up to 2000 mg/d are safe for use by the general population. Many clinical trials show the safety of combinations of vitamins E and C at the amounts identified for their independent UL values.

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