OPINION OF THE SCIENTIFIC COMMITTEE ON FOOD ON THE TOLERABLE UPPER INTAKE LEVEL OF VITAMIN E

(EXPRESSED ON 4 APRIL 2003)

FOREWORD

This opinion is one in the series of opinions of the Scientific Committee on Food (SCF) on the upper levels of vitamins and minerals. The terms of reference given by the European Commission for this task, the related background and the guidelines used by the Committee to develop tolerable upper intake levels for vitamins and minerals used in this opinion, which were expressed by the SCF on 19 October 2000, are available on the Internet at the pages of the SCF, at the address: http://www.europa.eu.int/comm/food/fs/sc/scf/index_en.html.

1. INTRODUCTION

Vitamin E is the term used to describe a group of related fat-soluble tocochromanols, including eight naturally occurring components, which exhibit antioxidant activity and are nutritionally essential. The two major homologous series of tocochromanols, the tocopherols and tocotrienols, both have vitamin E activity in humans and animals and are synthesised by higher plants and cyanobacteria.

In all homologues, the basic structural unit is a chroman ring system (2-methyl-6-hydroxychroman) with an isoprenoid side chain of 16 C atoms. The compounds, including α-, β-, γ-, and δ-homologues, differ in number and position of the methyl substituents in the chroman ring. Tocopherols differ from their corresponding tocotrienols in having a saturated side chain. The presence of the phenolic hydroxyl group in the tocochromanols is important for their activity as antioxidants. At least one methyl group in the benzene ring is of primary importance. α-Tocopherol with three methyl groups is the most active of all homologues, followed by β-, γ-, and δ-tocopherol. The only forms retained in human plasma are the RRR-α-tocopherol and the 2R-stereoisomers, RSR-, RRS- and RSS-α-tocopherol; the various 2S-stereoisomers (SRR-, SSR-, SRS- and SSS-α-tocopherol) which form part of synthetic *all rac*-α-tocopherol are not maintained in plasma (Traber, 1999). The vitamin E activity is expressed as *RRR*-α-tocopherol equivalents, which accounts for about 90% of the activity in human tissue; the relative potency of α-, β-, γ-, and δ-tocopherol is reported to be approximately 100:50:25:1. The commercially available synthetic form is all rac-α-tocopheryl acetate with the activity of 0.67 x *RRR*-α-tocopherol. For practical purposes, 1 International Unit (I.U.) of vitamin E is referred to as 1 mg of all rac-α-tocopheryl acetate (Schäfer and Elmadfa, 1984; Elmadfa and Leitzmann, 1998).

In the following report the term vitamin E is related to α-tocopherol equivalents.

2. NUTRITIONAL BACKGROUND

2.1. Occurrence in food

The major food sources of vitamin E are vegetable oils, unprocessed cereal grains, and nuts with smaller amounts in fruits and vegetables and meats (mainly the fatty portion).

2.2. Dietary intake of vitamin E

As indicated above, only the *RRR*-α-tocopherol from food and the 2*R*-stereoisomeric forms that occur in supplements and fortified foods are retained in the body because α-tocopherol transfer protein has an affinity only for these isomers . However, most nutrient data bases and survey data do not distinguish between the various tocopherols in food. Consequently, the data are presented as α-tocopherol equivalents which include all eight naturally occurring forms.

Table 1. Estimated intakes of vitamin E (mg TE/day)

Country	Type of survey	n	Method	Supplements*	Mean	97.5%
Austria[a]	Individual	2488	24h recall	Not defined	11.8	30.6
Germany	Individual (M) Individual (F)	854 1134	7-day dietary record	- -	14.6[b] 12.3[b]	33 28
UK[c]	Individual (M) Individual (F) Individual (M) Individual (F)	1087 1110 1087 1110	7-day weighed inventory	- - + +	9.9 (9.3) 7.2 (6.7) 11.7 (9.3) 8.6 (6.8)	19.5 15.2 23.4 20.4
Italy[d]	Household	2734	7-day record	+	11	22
Netherlands[e]	Individual	5958	2-day record	-	12.5	28.1
Ireland[f]	Individual (M) Individual (F)	662 717	7-day estimated food record	+ +	11.2 11.0	28.3 38.3

* + data included supplements; - data excluded supplements.
[a] Elmadfa *et al* (1998).
[b] Heseker *et al* (1994) - values are the median.
[c] Gregory *et al* (1990) - values are the mean with the median in parentheses.
[d] Turrini (1996).
[e] Hulshof and Kruizinga (1999).
[f] IUNA (2001).

2.3. Absorption and metabolism

The bioavailability of vitamin E is related to the efficiency of absorption. Intestinal absorption of lipids and fat-soluble vitamins depends on pancreatic function, biliary secretion to form micelles with the hydrolysed fat, and transfer across intestinal membranes. Nearly all of the vitamin E absorbed across the intestinal mucosa is free tocopherol. *In vivo* and *in vitro* studies suggest that the rate of uptake of vitamin E is controlled by passive diffusion. Absorption of tocopherols is incomplete; the extent of absorption is dependent on intake and varies between 20-80%. The proportion absorbed decreases with increasing amount added to experimental diets; the average absorption is about 40-60% while pharmacological doses of 200 mg and more are absorbed to the extent of <10%.

Cannulation studies indicate that there is no difference in absorption between α-tocopherol and α-tocopheryl acetate at physiological doses. At high levels of intake, (>400 IU/day) a higher degree of absorption was obtained with free tocopherol than tocopheryl esters.

About 90% of the free α-tocopherol is transported via the lymphatic system into the bloodstream, where it is distributed into lipoproteins on passage into the liver. The main systemic transport system of tocopherols is the LDL-fraction (55-65%) followed by the HDL (24-27%) and VLDL (8-18%). There is very close correlation (r=0.925) between the total serum α-tocopherol and that portion carried by LDL.

2.4. Mode of action and nutritional requirements

The basic mode of action of tocopherols in human tissue is to prevent the oxidation of polyunsaturated fatty acids (PUFA) by trapping free radicals and donating hydrogen. It is effective in protecting the integrity of lipid and phospholipid in membranes and thus the requirement for vitamin E and the recommended intake is determined to a large extent by the intake of PUFAs. It has been shown that increasing the PUFA content of a diet low in α-tocopherol equivalents has adverse effects on tocopherol status (Horwitt, 1974; SCF, 1993).

In human metabolism, vitamin E is known to interact with other nutrients which are also involved in the pathways of oxidation processes. Vitamin C, selenium and zinc interact synergistically with vitamin E. Conversely, an iron overload is associated with a lowering of serum vitamin E levels.

Results from animal models and epidemiological studies in humans suggest that vitamin E may protect against cancer. The most consistent associations have been reported for cancers of the lung, oesophagus and colorectum. Three intervention trials showed an inverse rel;ationship between vitamin E intake and cancer risk: LINXIAN study (Blot *et al*, 1993), ATBC study (Heinonen *et al*, 1998) and

Polyprevention study (Greenberg *et al*, 1994). However, in the LINXIAN study, the protective effect for oesophageal and gastric cancer was associated with co-administration of vitamin C, E and selenium and in the Polyprevention study there was no effect on the incidence of colorectal adenomas. The ATBC study did show a protective effect of vitamin E on mortality from prostate cancer.

Although the evidence is stronger for prevention of coronary heart disease, only one of four double-blind, placebo-controlled trials, the Cambridge Heart Antioxidant Study (CHAOS), had a positive result (Stephens *et al*, 1996). Two other trials (the GISSI-Prevenzione Trial and the Heart Outcomes Prevention Evaluation [HOPE] Study) were neutral (GISSI-Prevenzione Investigators 1999 and HOPE study Investigators 2000). In addition, the ATBC Cancer Prevention Study reported no beneficial effects on myocardial infarction rates (ATBC Cancer Prevention Study Group, 1994).

In a recent placebo-controlled trial of the effect of antioxidant vitamin supplementation in 20536 high-risk individuals aged 40-80 years, vitamin E (600 mg) was administered along with vitamin C (250 mg) and beta-carotene (20 mg) daily over a 5 year period. There were no significant differences in all-cause mortality nor deaths due to vascular or non-vascular causes. There were no effects on cancer incidence nor on hospitalisation for an other cause. The study group concluded that in this group, these vitamins were safe but were ineffective in producing significant reduction in 5-year mortality from any cause (Heart Protection Study Collaborative Group, 2002)

A randomised controlled trial was conducted in 1193 healthy volunteers aged 55-80 years to determine whether vitamin E supplementation (500 IU daily) influenced the incidence or rate of progression of age-related maculopathy. After 4 years there was no indication that vitamin E prevented the development of macular degeneration (Taylor *et al*, 2002)

2.5. Vitamin E requirements

The major problem in making recommendations for vitamin E is the dependence on the PUFA intake. Across Europe there are wide variations in PUFA consumption. The intakes are normally distributed but high values are common. Based on the strong relation between vitamin E requirements and PUFA, recommendations have to take into account the different intake of PUFAs in different population groups. Therefore the recommended intakes are given as the ratio mg α-tocopherol equivalents: 0.4 mg x g dietary PUFA. There is no evidence that this level is inadequate for anyone, and it is used by several different countries and organisations (SCF, 1993; Yasuda, 1993; D-A-CH Referenzwerte, 2000). In view of the difficulty in recommending the amount of vitamin E with the optimal effects on human metabolism, the recommendations for vitamin E expressed as α-tocopherol equivalents for adults differ world-wide.

Several double-blind placebo-controlled trials of the efficacy of supplementary vitamin E in preventing or ameliorating CHD are currently in progress but the US Food and Nutrition Board of the National Academy of Science concluded that the evidence presently available does not allow recommendations for higher intakes of vitamin E to be made.

2.6. Nutritional status for vitamin E

Normal plasma vitamin E concentrations in humans range from 12-45 μM (0.5-2 mg/dL). The most important factor influencing the vitamin E plasma concentrations appears to be the content of total lipids. The plasma concentrations alone, however usually do not directly reflect the intake of vitamin E and there is a strong correlation between vitamin E intake and fat intake (Bramley *et al*, 2000).

2.7. Vitamin E deficiency

Vitamin E deficiency in animals is associated with a progressive necrosis of the nervous system and muscle. Chronic marginal deficiency can be generally characterised by an enhanced susceptibility to lipid peroxidation and corresponding lipofuschinosis. In rats this first results in weakening of the basement membranes of the muscle capillaries and a breakdown of endothelial cells. Later, a subendothelial fibrosis arises in combination with fibrous and calcified lesions and necrosis in the media of the aorta. In piglets, vitamin E deficiency leads to a combination of myocardial necrosis with widespread thrombosis of the myocardial circulation.

2.7.1. Sensitive sub-populations

In humans, vitamin E deficiency causes a proliferative vasculopathy in premature, neonatal infants, neuropathological disturbances, cardiomyopathy and haematological disorders in children and adults (for review see Elmadfa and Bosse 1985; Gey, 1993).

As vitamin E is a component of many different foods, a deficiency arising from low dietary intake is improbable. Therefore the ratio of 0.4 mg α-tocopherol equivalents per g dietary polyunsaturated fatty acids expressed as dienoic acid, is valid, provided that the intake does not fall below 4 mg/d for adult men and 3 mg/d for adult women (SCF, 1993; Elmadfa and Leitzmann, 1998).

The sub-populations most likely to have a deficiency of vitamin E are:

- Premature infants and full-term infants of low birth weight (<2500 g);
- Patients with gastrointestinal or hepatic disorders with malabsorption syndromes;
- Subjects with A-β-lipoproteinaemia.

Especially in low-birth-weight infants, iron administration may lead to the development of vitamin E-deficiency anaemia (Melhorn and Gross, 1971; Dallman, 1974), particularly in infants who are also fed a high PUFA formula. These infants are also known to be more susceptible to oxygen injury but without having a high storage capacity and thus have higher vitamin E requirements in ratio to their body weight (D-A-CH Referenzwerte, 2000).

3. HAZARD IDENTIFICATION AND CHARACTERISATION

3.1. Toxicological data in animals

3.1.1. Acute toxicity

Vitamin E has a very low acute oral toxicity. The LD_{50} for α-tocopherol *per se* is greater than 2000 mg/kg body weight in mice, rats (adult and neonate) and rabbits and for the succinate ester it is >7000 mg/kg body weight for young adult rats of both sexes (Krasavage and Terhaar, 1977).

3.1.2. Sub-chronic toxicity

In rats given α-tocopheryl acetate by gavage at doses of 125-2000 mg/kg bw/day, TSH levels were elevated by 30-100%. At a dose of about 500 mg/kg bw/day biochemical indices of hepatotoxicity (serum alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase) were elevated and liver weight was increased. The NOAEL for these effects was 125 mg RRR-α-tocopheryl acetate/kg body weight (Abdo *et al*, 1986).

3.1.3. Chronic toxicity

Two long-term studies of up to 16 months and 2 years duration respectively have been conducted in rats (Yang and Desai, 1977; Wheldon *et al*, 1983). In the second of these studies, the animals received doses of 500, 1000 or 2000 mg dl-α-tocopheryl acetate/kg bw/day. At all dose levels between 15 and 18 weeks the male animals developed spontaneous haemorrhages in the gut, urinary tract, meninges, orbit and at sites of minor injury. This led to some mortality but in survivors the condition was corrected by administration of 10 mg vitamin K_3/kg body weight. The only other treatment-related effect of significance was the presence of vacuolated lipid staining macrophages in the liver.

Vitamin E displayed no evidence of carcinogenicity in either study. However, a NOEL could not be established in the latter study with respect to effects on blood clotting and liver histology (WHO, 1986).

3.1.4. Reproductive toxicity/teratogenicity

The results of reproductive toxicity studies in rats indicated that vitamin E (administered as the water-soluble d-α-tocopherol (polyethylene glycol 1000 succinate) did not have adverse effects on reproductive function at doses of up to 2% of the diet (Krasavage and Terhaar, 1977) and d-α-tocopherol was not teratogenic in mice (Hook *et al*, 1974).

3.1.5. Genotoxicity

No studies designed to investigate the potential genotoxicity of vitamin E *per se* were identified. However, in studies of the modulating effect of vitamin E on the mutagenicity/clastogenicity of other genotoxic compounds, there were no indications of genotoxicity in vitamin E controls.

In investigations of the potential anticlastogenic activity in human lymphocytes *in vitro*, vitamin E did not induce chromosomal damage or sister chromatid exchange (Gebhart *et al* 1985).

In the *Salmonella typhimurium* assay, dl-α-tocopherol caused a significant decrease in point mutations induced by malonaldehyde or beta-propiolactone (Shamberger *et al* 1979).

In a sex-linked recessive lethal mutation assay in Drosophila, alpha-tocopheryl acetate in the nutrient medium at 500 IU/kg did not affect the mutation rate in irradiated males but caused a significant reduction in lethal mutations in subsequent generations bred from unirradiated females (Beckmann *et al* 1982).

3.2. Human studies

There are many reports in the literature dealing with the toxicity of vitamin E in human subjects. It is important to distinguish between these studies in degree and reliability. Some papers report a single observation on one subject, others planned studies with placebos with and without double blinding.

It is noted that inconsistent adverse effects of vitamin E were observed in the uncontrolled studies (Kappus and Diplock, 1992; Diplock, 1995).

One of the reported adverse effects concerns decreased blood coagulation. In a published case report, a prolonged bleeding time was found during chronic warfarin therapy in a man taking 800 mg α-tocopherol equivalents (1200 IU) (Corrigan and Ulfers, 1981). But in a more recent study neither 537mg α-tocopherol equivalents (800 IU) nor 800 mg α-tocopherol equivalents (1,200 IU) were found to influence prothrombin time. None of the test subjects who received vitamin E had a significant change in the bleeding time, so the authors concluded that vitamin E might safely be given to patients who require chronic warfarin therapy (Kim and White, 1996). Studies with healthy humans with vitamin E supplementation have shown that there are no changes in platelet aggregation or adhesion with daily vitamin E intake up to 800 mg α-tocopherol equivalents (1,200 IU) (Farrell and Bieri, 1975; Tsai *et al*, 1978; Steiner, 1991; Steiner, 1993).

It has also been reported, that 604 mg α-tocopherol equivalents (900 IU) per day did not influence the coagulation activity in persons who did not take any anticoagulant drugs (Kitagawa and Mino, 1989). The question of bleeding time was studied by Meydani *et al* (1998) who found no adverse effects, including the bleeding time, after a 4-month daily supplementation with 60, 200 or 800 IU (40, 134 or 537 mg α-tocopherol equivalents) vitamin E. Some other intervention trials were reported to show benefit against heart disease with higher vitamin E doses up to 800 IU = 537 mg α-tocopherol equivalents (Stampfer and Rimm, 1995; Stephens *et al*, 1996) but this observation has not been shown consistently.

The studies considered of most scientific value with adequate controls are presented in Table 2.

Table 2. Studies with oral vitamin E in human subjects with strict controls

Reference	Subjects	Dose/duration	Results
Farrell and Bieri, 1975	N = 28 adults	67-537 mg TE*/d 4 mo-21 yr (mean 2.9 yr) (100-800 IU α-tocopherol)	No evidence of toxicity by clinical chemical blood analysis
Ernst and Matrai, 1985	N = 16 adults	536 mg TE/d 4 wk (800 mg/d all rac-α- tocopheryl-acetate)	No adverse effects by clinical chemical blood analysis
Corrigan, 1982	N = 12 warfarin-treated cardiology patients	67-269 mg TE/d 4 wk (100-400 IU all rac α-tocopherol)	Warfarin effect was intensified

* TE: α-tocopherol equivalents

Regarding controlled double blind studies of vitamin E toxicity in humans, several reports exist that vitamin E has low toxicity and no consistent adverse effects, and these studies are reported in Table 3.

The principal negative effect observed was on prothrombin time or other factors related to blood clotting. In several studies no effects were reported but in others there were effects on blood clotting and it was claimed that high doses of vitamin E only influenced blood clotting in cases of low vitamin K status (Steiner, 1991; Steiner, 1993; Diplock *et al*, 1998). The published reports (Elmadfa, 1985; Kappus and Diplock, 1992; Meydani *et al*, 1998) concluded that vitamin E at high dietary intakes affects blood coagulation if vitamin K status is inadequate. High doses of α-tocopherol affected the vitamin K metabolism by reducing the cyclooxygenase pathway and therefore thromboxane synthesis, thus impairing the thromboxane-dependent blood coagulation and also decreasing the coagulation factor II and VII. It was suggested that high doses (800-1200 α-tocopherol equivalents) should be avoided for two weeks prior to and following surgery (Elmadfa and Bosse, 1985). In a critical comment on the high upper level for vitamin E of 1000 mg/day derived by the US Food and Nutrition Board (Horwitt, 2001) attention was drawn to the observation that the tendency to haemorrhage in aspirin users is increased by vitamin E (Liede *et al,* 1998).

Table 3. Double blind control studies with oral vitamin E in humans

Reference	Subjects	Dose/duration	Results
Anderson *et al*, 1974	N = 38 Angina pectoris patients	2362 mg TE*/d 9 wk (3200 mg RRR-α-tocopheryl succinate)	No adverse effects except some gastrointestinal disturbance (diarrhoea: 3 subj; intestinal spasm)
Bierenbaum *et al*,1985	N = 25 Diabetic subjects	1820 mg TE/d (2000 mg all rac-α-tocopheryl acetate)	No adverse effects by clinical chemical blood analysis (cholesterol, T^3, T^4, blood coagulation)
Gillilian *et al*, 1997	N = 52 Angina pectoris patients	1322 mg TE/d 6 mo (1600 IU RRR-α-tocopheryl succinate)	No adverse effects in cardiac function parameters, urinalysis, blood count, blood chemistry, prothrombin time
Kitagawa and Mino, 1989	N = 19 adults	600mg TE/d 12 wk (600mg α-tocopherol)	No objective or subjective adverse effects
Stampfer *et al*, 1983	N = 30 volunteers	550mg TE/d 16 w (800 IU α-tocopherol)	No group differences
Tsai *et al*, 1978	N = 202 volunteers	441 mg/d TE 4 w (600 IU α-tocopheryl acetate)	Serum T^3 and T^4 lower; no adverse effect
Meydani *et al,* 1998	N = 88 healthy volunteers aged >65 years divided between control and three dose groups (17-19 per group)	60, 200 or 800 IU/d for 4 months	No subjective side effects No effect on GSH peroxidase, superoxide dismutase, immunoglobulin, anti-DNA or thyroglobulin antibodies, body weight, total plasma proteins, albumin, glucose, lipids or lipoprotein profile, total bilirubin, serum liver enzymes, blood count, platelet number, bleeding time, Hb, haematocrit, urinary or serum creatinine

* TE: α-tocopherol equivalents

The effects on blood clotting are not, however, the only adverse effects requiring consideration. Side effects reported in therapeutic use of vitamin E supplements include severe muscular weakness and fatigue induced in adults receiving daily doses of 720 mg α-tocopherol (Cohen, 1973). These side

effects were confirmed in a double-blind study on two healthy male subjects given the same dose of α-tocopherol and the symptoms were associated with a large increase in 24 hr urinary creatinine and elevated serum creatine phosphokinase (Briggs, 1974; Briggs and Briggs, 1974).

When patients with porphyria cutanea tarda were given daily doses of 1.0 g α-tocopherol for 3 months there was a marked increase in 24 hour urinary androgens (androsterone, etiocholanolone plus dehydroepiandrosterone) from 3.5 to 4.6 mg/day while mean 24 hour pregnanediol fell from 2.2 to 0.5 mg/day (Pinelli *et al*, 1972). The authors concluded that the significance of these endocrine changes was uncertain but could be important for patients with endocrine sensitive tumours.
Vitamin E has been reported to cause an increase in iodine uptake by the thyroid and in serum organic iodine at doses of 400-500 mg/day of TE for 4 weeks but this was apparently asymptomatic and not associated with an increase in BMR (Tsai *et al*, 1978).

A group of 52 elderly patients (average age 72 years) showed an average increase in serum cholesterol of 74 mg/dL when given repeated daily doses of 300 mg α-tocopherol (Dahl, 1974). Conversely, no such increase was seen in a small group of healthy men taking 588 mg (800 I.U.) daily (Briggs, 1974).

3.2.1. Epidemiological evidence

There are limited data relating to the effects of vitamin E on morbidity and mortality from chronic diseases.

In the ATBC study (1994) an increase was observed in the numbers of deaths from haemorrhagic stroke among male smokers. Although the number of haemorrhagic stroke cases with 50 mg α-tocopherol was 66 compared to 44 in the control group (total n = 29,133) no statistical significance was published. A more recent analysis of this study indicated that there was an increased risk of subarachnoidal haemorrhage in hypertensive men (RR 2.45; CI 1.08-5.55) and a significantly higher mortality. Gingival bleeding occurred more frequently in subjects who were also taking aspirin (Leppala *et al* 2000 a and b; Liede *et al*, 1998). In two other studies, the Secondary Prevention with Antioxidants of Cardiovascular Disease in endstage renal disease (SPACE) and the Primary Prevention Project (Boaz *et al* 2000; Collaborative Group of the Primary Prevention Project, 2001) there was a non-statistically significant increase in fatal haemorrhages.

4. DERIVATION OF A TOLERABLE UPPER INTAKE LEVEL (UL)

4.1. Adults

The establishment of a NOAEL depends on the interpretation of asymptomatic effects on clinical biochemical parameters reported in some human studies and supported by similar effects in experimental animals. No NOAEL could be established from the chronic toxicity studies in the rat with respect to blood clotting and liver histology. Consequently, in considering food additive use, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) derived an ADI for dl-α-tocopherol of 0.15-2 mg/kg body weight based on clinical experience in humans (WHO, 1986). The SCF reviewed the data on tocopherol extracts, α-, β-, γ- and δ-tocopherol and α-tocopheryl acetate and concluded that their use as antioxidants in food was acceptable and that it was not appropriate to establish an ADI (SCF, 1989).

In considering the derivation of a tolerable upper intake level the present Committee considered that the asymptomatic effects on biochemical indices (urinary steroid hormones, I_2 metabolism), were of doubtful toxicological significance and the reports of fatigue associated with effects on creatine phosphokinase and increased urinary creatine were limited in duration and involved only two subjects. These observations have not been reproduced in other studies. The Committee therefore decided that the critical effect is on blood clotting and that the study by Meydani *et al* (1998) provided the best basis for an evaluation of the tolerable upper intake level. The NOAEL established in this study was 540 mg/day.

Considering the above the Committee concluded that an uncertainty factor of 2 would adequately cover interindividual differences in sensitivity. A larger uncertainty factor was not considered necessary because data from a number of other older but less well controlled studies showed no adverse effects at considerably higher intakes. The UL for vitamin E was therefore established as 270 mg/day for adults and rounded to 300 mg/day.

4.2. Pregnancy and Lactation

The Committee considered that the UL applied also to the women during pregnancy and lactation based on no indication from animal studies of special risk during this period.

4.3. Children and adolescents

There are no data specifically relating to children and adolescents. The UL for children and adolescents is derived by scaling the adult UL on the basis of body surface area (body weight$^{0.75}$).

Age (years)	Tolerable Upper Intake Level (UL) for vitamin E (mg per day)
1-3	100
4-6	120
7-10	160
11-14	220
15-17	260

5. CHARACTERISATION OF RISK

Current estimated intakes from food and supplements, including the 97.5th percentile, in the population are generally well below the UL. However, some users of high dose supplements may exceed the UL.

Oral intakes of high amounts of vitamin E can increase the blood coagulation defects in subjects with vitamin K deficiency caused by malabsorption or due to therapy with anticoagulants. Therefore the UL is not considered to apply to patients receiving anticoagulant drugs or to patients with malabsorption syndromes, nor to other conditions where the synthesis of vitamin K by the gut microflora might be impaired. In addition there is evidence that vitamin E can increase the risk of haemorrhage in individuals taking aspirin.

6. REFERENCES

Abdo KM, Rao G, Montgomery CA (1986). Thirteen week toxic study of d-αtocopheryl acetate (vitamin E) in Fischer 344 rats. Fd Chem Toxic 24: 1043-1050.

Anderson TW and Reid DB (1974). A double-blind trial of vitamin E in angina pectoris. Am J Clin Nutr 27: 1174-1178.

Beckmann C, Roy RM, Sproule A (1982) Modification of radiation-induced sex-linked recessive lethal mutation frequency by tocopherol. Mut Res 105: 73-77.

Bierenbaum ML, Nooan FL, Machlin LJ, *et al* (1985). The effect of supplemental vitamin E on serum parameters in diabetics, postcoronary and normal subjects. Nutr Res Int 31: 1171-1180.

Blankenhorn G and Clewing S (1993). Human studies of vitamin E and rheumatic inflammatory disease. In: Vitamin E in Health and Disease (eds: Packer L and Fuchs J). Marcel Decker, New York.

Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, Yang CS, Zheng SF, Gail M, Li GY, *et al* (1993). Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J Natl Cancer Inst 85: 1483-1492.

Boaz M, Smetana S, Weinstein T, Matas Z Gafter U, Iaina A, Knecht A, Weissgarten Y, Brunner D, Fainaru M, Green MS (2000). Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomised placebo-controlled trial. Lancet 356: 1213-1218.

Bramley PM, Elmadfa I, Kafatos A, Kelly FJ, Manios Y, Roxborough HE, Schuch W, Sheehy PJA, Wagner K-H (2000). Vitamin E. Journal of the Science of Food and Agriculture 80: 913-938.

Briggs MH and Briggs M (1974). Are vitamin E supplements beneficial? Med J Aust 1: 434-437.

Briggs MH (1974). Vitamin E supplements and fatigue. N Engl J Med 290: 579-580.

Cohen HM (1973). Fatigue caused by vitamin E? Calif Med 119: 72.

Collaborative Group of the Primary Prevention Project (PPP) (2001). Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice. Lancet 357: 89-95.

Collins DL, Davies PSW, Hughes JM, Clarke PC (1995). Nutrition Survey: children aged 1½ to 4½ years: Volume 1, Report of the diet and nutrition survey, London, HMSO.

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

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

Dahl S (1974). Vitamin E in clinical medicine. Lancet 1: 465.