# Risk Assessment — Vitamin E

## General information

### Chemistry

The term vitamin E is used as a generic designation for a group of eight lipid-soluble compounds synthesised by plants. These compounds fall into two classes, tocopherols and tocotrienols, which exhibit the biological antioxidant activity of vitamin E. Vitamins in both classes are designated by the Greek letters α, ß, γ and δ. The most biologically active antioxidant is *d*-α-tocopherol. Vitamin E activity is expressed as *d*-α-tocopherol equivalents. Where activity is given as International Units (IU), 1 IU of *d*-α-tocopherol (RRR-α-tocopherol) is equivalent to 0.67 mg. If the vitamin E is present in the form of *dl*-α-tocopherol (*all-rac*-α-tocopherol), then 0.91 mg is equivalent to 1 IU.



### Natural occurrence

Vitamin E is synthesised only by plants and is, therefore, found primarily in plant products, the richest source being plant oils. All higher plants (that is plants other than algae) appear to contain α-tocopherol in leaves and other green parts, while γ-tocopherol is generally present in lower concentrations. Animal tissues tend to have low concentrations of vitamin E, with the highest levels occurring in fatty tissues though this varies according to the intake of vitamin E.

### Occurrence in food, food supplements and medicines

Plant oils are the main dietary sources of vitamin E (560-1600 mg/kg in soybean oil, 530-1620 mg/kg in corn oil and 50-150 mg/kg in olive oil), with meat (0.5-1.6 mg/kg), poultry (1.6-4.0 mg/kg) and dairy products (0.4-10.0 mg/kg) providing only moderate amounts. The amount of vitamin E in foods at the point of consumption is difficult to assess as it depends upon the effects of processing, storage and preparation. Vitamin E is present in a variety of dietary supplements at doses of up to 268 mg/day in multi-constituent products and 670 mg/day in single constituent products. Vitamin E is also present in licensed medicinal products; the highest doses authorised are 20-100 mg.

### Recommended amounts

Foods containing large amounts of polyunsaturated fatty acids (PUFAs) will generally contain large amounts of vitamin E. In addition, the requirement for vitamin E increases with the amount of dietary PUFAs consumed. Thus, owing to the widely differing requirements based on the PUFA intake, it is generally considered more realistic to give ranges of acceptable intake rather than a fixed level. Using this approach, in a NDNS survey (Gregory *et al*, 1990) of 1629 adults only 0.7% had serum tocopherol:cholesterol ratios lower than 2.25 μmol/mmol (below this erythrocytes have a tendency to haemolyse). The 2.5 and 97.5 centile intakes were 3.5 mg and 19.5 mg in men and 2.5 mg and 15.2 mg in women. This gives a median intake of 9.3 mg α-tocopherol equivalent/day for men and 6.7 mg/day for women. COMA considered these ranges and concluded that daily intakes of 4 mg and 3 mg of α-tocopherol equivalents could be adequate for men and women respectively (COMA, 1991). Potential deficiency, however, could be excluded if the lower intakes are maintained over prolonged periods. Intakes of 3.8 – 6.2 mg/day appear to be satisfactory for pregnant and lactating women.

### Analysis of tissue levels and vitamin E status.

Measurement of serum plasma concentration of α-tocopherol provides the simplest and most direct evidence of vitamin E status. Values of 5 – 20 μg/mL for adults and children of twelve years or older and values of 3 – 15 μg/mL for children under twelve years indicate acceptable levels of intake. Another widely used indicator of vitamin E status is the extent of haemolysis of red blood cells in the presence of hydrogen peroxide. A high degree of haemolysis accompanies vitamin E deficiency (i.e. greater than 20%); however, this is not specific to vitamin E deficiency.

### Brief overview of non-nutritional beneficial effects.

It has been claimed that vitamin E can prevent free radical damage. In a cancer prevention study, the incidence of prostate cancer was 32 % lower and mortality was 41 % lower in men taking α-tocopherol, either with or without ß-carotene, than in those not taking the vitamin supplement. Vitamin E is thought to have a role in the prevention of atherosclerosis, through inhibition of oxidation of low-density lipoprotein. Vitamin E has been reported to relieve the symptoms of fibrocystic breast disease. It has also been claimed that menopausal symptoms may be relieved by vitamin E.

Vitamin E has been used to treat scleroderma and it has been reported that it may prevent retrolental fibroplasia and intracranial haemorrhage in premature infants. In animal studies, vitamin E has been found to reduce UV-induced acute and chronic skin damage.

### Function

It is unclear whether vitamin E functions solely as a lipid antioxidant, or whether it might also be required for the function of some other critical, but unknown metabolic factor. However, current information suggests that the effects of vitamin E are consistent with an antioxidant role. In this regard, vitamin E is thought to have basic functional importance in the maintenance of membrane integrity in virtually all cells of the body. Non-antioxidant functions have also been proposed for α- but not ß-tocopherol including modification of gene transcription and expression.

### Deficiency

The clinical manifestations of vitamin E deficiency vary considerably between species. In general, the targets are the neuromuscular, vascular and reproductive systems. The various signs of vitamin E deficiency are believed to be manifestations of membrane dysfunction, resulting from oxidative degradation of polyunsaturated membrane phospholipids and/or the disruption of other critical cellular processes.

### Interactions

Vitamin E may exacerbate the effects of vitamin K deficiency, thus affecting blood coagulation. This has been reported in animal studies and in case reports of humans taking large doses the basis for the interaction is unclear. Vitamin E may also interfere with vitamin A absorption.

### Absorption and bioavailability

α-Tocopherol is absorbed unchanged from the small intestine by non-saturable, passive diffusion. Tocotrienol esters are first hydrolysed by pancreatic esterase. Absorption appears to occur mostly in the upper and middle thirds of the small intestine. The absorption efficiency of tocopherol and its esters is generally considered to be variable. It has been reported that in human studies, absorption of α-tocopherol and its acetate ester was in the region of 21 – 86% over 24 hours.

### Distribution and metabolism

Vitamin E does not appear to have a specific carrier protein in the plasma, but it is rapidly transferred from chylomicrons to plasma lipoproteins, to which it binds non-specifically. The vitamin is taken up by the liver and released in low density lipoprotein (LDL). Most absorbed tocopherols are transported unchanged to the tissues. Kinetic studies indicate that the body has two pools of the vitamin: a 'labile' pool which turns over rapidly and a 'fixed' pool which turns over slowly. The labile pool predominates in tissues such as plasma and liver, as the tocopherol contents of those tissues are depleted rapidly under conditions of vitamin E deprivation. In contrast, the adipose vitamin E resides predominately in the bulk lipid phase, which appears to be a fixed pool of the vitamin.



### Excretion

At normal intake levels, vitamin E is conjugated with glucuronic acid and this conjugate is excreted (via bile) in the faeces. Up to 30-70 % of vitamin E is excreted via this route with less than 1% being excreted in the urine. Some vitamin E may be eliminated via the skin.

## Toxicity

### Human data

Vitamin E has low toxicity. Humans and animals appear to be able to tolerate levels of the vitamin two orders of magnitude above nutritional requirements, e.g. 1000 – 2000 IU/kg diet without untoward effects. At very high doses, however, vitamin E can produce signs indicative of antagonism with the function of the other fat-soluble vitamins (vitamins A, D, K). Isolated reports of adverse effects in humans consuming up to 1000 IU of vitamin E per day include headache, fatigue, nausea, double vision, muscle weakness, mild creatinuria and gastrointestinal distress.

In the Alpha-Tocopherol, Beta-Carotene (ATBC) study, vitamin E supplementation was associated with an increased risk of mortality from haemorrhagic stroke, whilst in the Cambridge Heart Antioxidant Study (CHAOS) a small excess of cardiovascular deaths was observed in the supplemented group. These are described below:

*Supplementation studies*

Many human studies, both small and large scale, have considered the effect of vitamin E on various biochemical and physiological parameters. These have included large-scale intervention studies, designed to assess the effects of vitamin E on conditions such as cancer and heart disease, which have not generally considered more minor side effects. In smaller scale trials, few adverse effects have been reported. However, creatinuria, breast pain, diarrhoea and fatigue and dizziness have been noted in some investigations.

### Animal data

Animals with hypervitaminosis E have been found to show impaired bone mineralisation, reduced hepatic storage of vitamin A and coagulopathy. In each case, these signs could be corrected with increased dietary supplements of the appropriate vitamin (i.e. vitamins D, A and K, respectively). The antagonism appeared to occur during absorption.

### Carcinogenicity and genotoxicity

No carcinogenicity studies have been identified in laboratory animals, however, some limited chronic studies exist which do not suggest that vitamin E is carcinogenic. No *in vivo* or *in vitro* genotoxicity studies have been identified. Co-incubation with vitamin E has been reported to reduce the mutagenic effect of chemicals such as malonaldehyde and ß-propiolactone in some Ames test studies.



### Mechanism of toxicity

Vitamin E has been reported to interact with vitamin K. The mechanism of this is uncertain, but it has been suggested that the metabolite tocopherylquinone, which is structurally similar to vitamin K may inhibit vitamin K metabolism and thus coagulation.

### Dose-response characterisation

No relevant data have been identified.

### Vulnerable groups

No vulnerable groups have been identified.

### Genetic variations

Familial isolated vitamin E deficiency is a rare autosomal recessive neurodegenerative disorder with symptoms similar to those of Friedrich's ataxia. Supplementation with vitamin E can prevent the onset of the disease if given before irreversible damage occurs.

## Studies of particular importance in the risk assessment

(For full review see http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers or the enclosed CD).

*Gillilan et al., 1977*

Forty-eight patients with stable angina completed a double-blind crossover study of two 6 month periods of treatment with 1600 IU/day *d*-α-tocopherol succinate (equivalent to 1072 mg *d*-α-tocopherol) or placebo. No statistically significant differences were apparent in a number of cardiac parameters including systolic time interval assessment of left ventricular function and the multistage,

maximal exercise test. The subjects were questioned regarding possible side effects and underwent periodic urinalysis, blood count and blood chemistry analysis, measures of prothrombin time, chest X-ray and ECG. No deleterious side effects were observed. There was a slightly increased incidence of gastrointestinal disturbance during the placebo phase; further details are not provided. It was stated that there was 'no exacerbation of hypertension, congestive heart failure or skeletal muscle complaints could be attributed to vitamin E therapy'. No further details are provided. No differences were found in the various clinical chemistry indices.

*Cambridge Heart Antioxidant Study (CHAOS): Stephens et al., 1996*

2002 patients with atherosclerosis were entered into a double-blind placebo-controlled study and followed up for a median of 510 days (range 3-981). The treatment group received a dose of 800 IU vitamin E (537 mg as *d*-α-tocopherol)/day for the first 546 patients and 400 IU/day (268 mg as *d*-α-tocopherol)/day for the remainder. Treatment significantly reduced the risk of cardiovascular death and non-fatal myocardial infarction (MI) (a composite endpoint). However, this decrease was due to the decrease in MI since, when separated out, there was a slight non-significant excess of cardiovascular deaths in the treatment group (RR, 1.18, 95% CI, 0.62-2.27, p=0.61). The authors speculated that the finding might be due to chance or might reflect a difference in biological events leading to death and those leading to non-fatal MI and noted that the results of larger studies would be necessary to clarify this. The study was not designed to look at any dose response effects and there was no randomisation of the subjects within the different treatment groups.

*Meydani et al., 1998*

Eighty-eight healthy older subjects (aged > 65 years) were entered into a double-blind placebo-controlled study, receiving placebo, 60, 200 or 800 IU *dl*-α-tocopherol/day (34, 134 or 537 mg *d*-α-tocopherol equivalents) for four months. The groups contained 17, 19, 18 and 19 subjects respectively. The study was designed to assess the effect of supplementation on general health and measured an extensive range of parameters. It was stated that no side effects were reported. Supplementation had no effect on plasma concentration of other anti-oxidant vitamins and minerals, glutathione peroxidase, superoxide dismutase or total cysteine. There was no significant effect of vitamin E on serum non-specific immunoglobulin concentrations or anti-DNA and anti-thyroglobulin antibodies. The cytotoxic ability of neutrophils against *Candida albicans* was not compromised. Vitamin E had no effect on body weight, plasma total proteins, albumin, glucose, plasma lipids or the lipoprotein profile, total bilirubin, serum liver enzymes, blood count, platelet number, bleeding time, haemoglobin, haematocrit, urinary or serum creatine levels. The authors concluded that supplementation had no detrimental effect on health.

*Ascherio et al., 1999*

In the Health Professional Follow-up Study, 43,738 men were recruited and followed for up to 8 years. Vitamin E intake was assessed by food frequency questionnaire which included questions on supplement use. None of the subjects had cardiovascular disease or diabetes. A total of 328 strokes occurred: 210 ischaemic, 70 haemorrhagic and 48 unclassified. After adjustment, the relative risks for ischaemic and total stroke were not affected by vitamin E intake. The association of vitamin E with haemorrhagic stroke was also non-significant but the confidence intervals were wide. The authors concluded that vitamin E supplements did not affect stroke risk but that modest effects could not be ruled out.

*GISSI-Prevenzione Investigators, 1999*

11,324 patients who had survived recent myocardial infarction were randomly assigned supplements of n-3 PUFA (1 g daily), 300 mg vitamin E (as synthetic α-tocopherol), both or neither for 3.5 years. The primary combined efficacy endpoint was death, non-fatal myocardial infarction and stroke. Smokers and ex-smokers were evenly distributed through the groups. Vitamin E treatment had no effect on the combined or separate endpoints.

*ATBC study: The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group, 1994; Leppälä et al., 2000*

In a randomised, double-blind placebo-controlled study, a total of 29,133 Finnish male smokers were randomly assigned to one of four treatment groups: 50 mg *dl*-α-tocopherol/day (equivalent to 55 IU), 20 mg/day ß-carotene, both α-tocopherol and ß-carotene, or placebo. Follow-up continued for five to eight years. Lung cancer incidence was not affected by α-tocopherol treatment, but the incidence of prostate cancer was reduced. α-Tocopherol had no apparent effect on total mortality but was associated with an increase in mortality from haemorrhagic stroke (7.8 deaths per 10,000 person years in the α-tocopherol group versus 5.2 deaths per 10,000 person years in the no α-tocopherol groups). In contrast, deaths from ischaemic stroke and ischaemic heart disease were reduced in the α-tocopherol group. Subsequent analysis of the risk factors for stroke indicated that vitamin E increased the risk of sub-arachnoid haemorrhage (RR, 2.45, 95% CI 1.08-5.55) and decreased the risk of cerebral infarction (RR, 0.7: 95%CI 0.55-0.89) in hypertensive men but had no effect on normotensive men.

*HOPE study: Yusuf et al., 2000*

A total of 9,541 subjects (6996 men and 2545 women) aged 55 or over at high risk for cardiovascular events were enrolled in a trial with a 2 x 2 factorial design. The participants received either 400 IU vitamin E (from natural sources – no further details provided) or placebo and either ramipril or matching placebo for a mean of 4.5 years. The primary endpoint was a combination of myocardial infarction and stroke and death from cardiovascular causes. The secondary outcomes included unstable angina, congestive heart failure, revascularisation or amputation, death from any cause, complications of diabetes and cancer. There were no significant differences in the numbers of deaths from cardiovascular causes (RR 1.05; 95%CI 0.9-1.22) between those receiving vitamin E or placebo or in any of the secondary outcomes. There were no differences in adverse effects between the vitamin E and placebo group or in the numbers of patients who stopped taking the study medication. There was also no difference in the incidence of haemorrhagic stroke between the groups.

*Primary Prevention Project (PPP), 2001*

In a controlled open 2 x 2 factorial trial, 4495 people were randomised to receive low dose aspirin (100 mg/day) or no aspirin, and vitamin E (300 mg/day as synthetic α-tocopherol) or no vitamin E to investigate the prevention of cardiovascular events in people with one or more major cardiovascular risk factors (hypertension, hypercholesterolaemia, diabetes, obesity or family history). The mean follow up period was 3.6 years. The main combined endpoint was the cumulative rate of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. Predefined analyses included cardiovascular deaths, total deaths, and total cardiovascular events. Smokers and ex-smokers were evenly distributed through the groups. Vitamin E had no effect on any pre-specified endpoint.

*Heart Protection Study Collaborative Group, 2002*

In a randomised placebo-controlled trial of antioxidant vitamin supplementation, 20,536 high risk adults (those with coronary heart disease, other occlusive vascular disease or diabetes) were given a daily supplement of 600 mg *dl*-α-tocopherol (equivalent to 660 IU), 250 mg vitamin C and 20 mg ß-carotene or placebo for five years (Heart Protection Study Collaborative Group, 2002). No difference in all cause mortality was revealed. Compliance was 83% on average in each treatment group, adverse experiences were sought at each follow up visit (every 4 months for the first year and every 6 months thereafter) and no significant side effects were reported. It is unclear whether minor side effects were reported or investigated. There was no significant difference in the number having a haemorrhagic stroke. Current and ex-smokers were evenly distributed between groups.

## Exposure assessment

Total exposure/intake (as *d*-α-tocopherol equivalents):

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|---|---|
| Food | Mean: 8.5 mg/day<br>97.5 percentile intake: 18 mg/day (1986/7 NDNS) |
| Supplements | up to 670 mg/day (Annex 4) |
| Estimated maximum daily intake: | 18 + 670 = 690 mg/day |

No potential high intake groups have been identified.

## Risk assessment

Very high doses of vitamin E have been reported to cause a few sporadic adverse effects. These include headache, fatigue, gastrointestinal distress, double vision, muscle weakness and mild creatinuria. High levels of vitamin E may also antagonise the effects of the other fat-soluble vitamins. Vitamin E also has an anti-platelet and anti-coagulant effect. A number of human supplementation studies on vitamin E are available. Unexpected findings were apparent in two large trials, one concerned with heart disease (CHAOS), and one which considered a range of health endpoints in male smokers (ATBC). An increased risk of mortality from haemorrhagic stroke was found in the treatment group of the ATBC study; this was considered to be biologically plausible given the effect of vitamin E on platelets and the authors noted that this finding should be subject to careful review. The level of vitamin E supplementation involved (55 IU/day, equivalent to 37 mg *d*-α-tocopherol equivalents/day) was relatively low, being about 4 times the average daily dietary intake. It is possible, however, that an interaction might have occurred between vitamin E and smoking which was not apparent in the rest of the population studies. Further analysis of the data suggests that the effect was only apparent in hypertensive subjects. The CHAOS study reported a non-significant excess in deaths from cardiovascular disease in the treatment group; but the authors considered that this might be a chance effect. In the MRC/BHF, HOPE and PPP studies where subjects at high risk of cardiovascular events were given higher doses of vitamin E, similar effects were not reported. In the observational study of male health professionals (Ascherio *et al.,* 1999)

the relative risk of total and ischaemic stroke was not affected by vitamin E intake, and there was no significant association between haemorrhagic stroke and vitamin E intake. These large intervention studies do not report more minor side effects.

Other smaller human supplementation studies are available, but not all of these investigate side effects in detail.

A significant effect of vitamin E is potential interference with vitamin K. This has been demonstrated in animal studies and in isolated case reports of subjects taking large doses of vitamin E. However, the Meydani study did not find an increase in prothrombin time in subjects taking 800 IU/day vitamin E. Work with in-patients taking the anti-coagulant warfarin suggested similar results. However, there are few data on these haematological effects at higher doses, so it is not possible to establish a threshold.

As noted above, vitamin E has been reported to have adverse effects on clotting in animal studies. There are few other animal data on vitamin E.



## ESTABLISHMENT OF SAFE UPPER LEVEL

Key studies: Gillilan *et al.* (1977); Meydani *et al.* (1996); Stephens *et al.* (1996)

| | |
|---|---|
| NOAEL: | 800-1600 IU/day (540 – 970 mg *d*-α-tocopherol equivalents/day) |
| Uncertainty Factor: | 1 |
| Safe Upper Level consumption over a lifetime: | 800 IU (540 mg *d*-α-tocopherol equivalents/day) supplemental for daily vitamin E (equivalent to 9.0 mg/kg bw/day in a 60 kg adult) |

In the trials by Gillilan *et al.* (1977) and Meydani *et al.* (1996) the biochemical and physiological effects of vitamin E were investigated in some detail and the findings indicate that supplemental doses of 800 to 1600 IU/day are without apparent adverse effect. The results were derived from small groups that may not be representative, thus an additional uncertainty factor could be applied to account for inter-individual variation. However, the results of the larger CHAOS trial (Stephens *et al.,* 1996) support the view that 800 IU/day supplemental vitamin E would not result in any adverse effects and, taking the three studies together, no further uncertainty factors are necessary. A Safe Upper Level of 800 IU/day (540 mg *d*-α-tocopherol equivalents/day) supplemental vitamin E is recommended. This is equivalent to 9.0 mg/kg bw/day for a 60 kg adult. Assuming an intake of 18 mg/day from food, a total intake of 560 mg *d*-α-tocopherol equivalents/day would not be expected to result in any adverse effect. This is equivalent to 12.4 mg/kg bw/day.

A study in male smokers has suggested that 55 IU/day vitamin E (equivalent to 37 mg *d*-α-tocopherol equivalents/day) may increase the risk of mortality from haemorrhagic stroke in hypertensive subjects who smoked. Although biologically plausible, the significance of this finding is uncertain. It has not been repeated in other studies in subjects at high risk of cardiovascular events treated with higher doses of vitamin E (up to 600 mg/day); however, if it is an effect related to smoking there may have been too few smokers in these studies for any effect to be apparent. In addition, a large observational study of male health professionals did not report this association.

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