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On the opinion of the European Commission "Scientific Committee on Food" regarding the tolerable upper intake level of vitamin E (2003)

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Sirs, the European Commission Scientific Committee on Food (SCF) has recently published its opinion on the tolerable upper intake level (UL) of vitamin E. The UL was established as 270 mg/d for adults, rounded to 300 mg/d. Based on the rationale used by the SCF in their report [13] we feel that this decision is unjustified

SCF derivation of a UL

The derivation of the UL by the SCF is exclusively based on the study by Meydani et al. [10] who did not observe any adverse effects after supplementation with up to 800 IU (540 mg tocopherol equivalents (TE))/day for 4 months. However, this study was performed on elderly subjects (and thus is not a representation of the general population) and had relatively low subject numbers (n = 17–19). The SCF decided that the critical effect for deriving an UL for vitamin E was on blood clotting. Although increased clotting times have been demonstrated during vitamin E supplementation, it has been claimed that this phenomenon only occurs in individuals who have a low vitamin K status. There is a lack of knowledge as to the impact of vitamin E supplementation on clotting times in a general population. Hence, using clotting times as their critical effect is in itself flawed. The SCF used a No Observable Adverse Effect Level (NOAEL) of 540 mg, based on the Meydani study. However, this was actually the highest dose tested in the study; therefore, a true NOAEL was not established. The SCF applies an uncertainty factor of 2 on this NOAEL for inter-individual differences in sensitivity and, thus, establishes a UL of 270 (300 rounded) mg TE/day. The UK Food Standards Agency (FSA) Expert Group on Vitamins and Minerals has also recently established a UL for vitamin E [4]. Their report cites the same studies as the SCF, however combines a number of other studies to establish a NOAEL of 540–970 mg TE/d. The FSA used an uncertainty factor of 1 because the authors conclude from the Gillilan [3], Meydani [10] and Stephens [14] studies that "800 IU/d supplemental VE would not result in any adverse effects and, taking the three studies together, no further uncertainty factors are necessary." Since there are several other studies – even quoted by the SCF – in which similar or higher supplemental vitamin E doses have been used, the derivation of the UL by the SCF based on a single study [10] and ignoring other scientific literature is arbitrary and unjustified.

Additional studies pointing to a higher UL

Gillilan et al. [5] did not observe any deleterious side effects in 48 angina pectoris patients who completed a double-blind crossover study of two 6-month treatment periods with vitamin E (1322 mg TE/day) and placebo. In particular – as mentioned in the SCF Opinion –, they did not find any adverse effects on prothrombin time, blood counts and blood chemistry in this relatively high-risk group.

In addition, a study by Bierenbaum et al. [2] in 25 diabetic subjects with 1346 mg TE/day also did not reveal any adverse effects by chemical analysis or blood coagulation.

In a study by Anderson et al. [1] with a daily dosage of 2592 mg TE/day over up to 9 weeks, lower gastrointestinal symptoms (severe cramps in 1 patient, diarrhoea in 3 patients) "appeared to be related to the ingestion of large doses of vitamin E". Thus, this dosage might be considered as a LOAEL in humans. Other adverse effects were not reported with this high dose.

Sano et al. [12] reported a study in which 170 Alzheimer's disease patients received vitamin E (1820 mg TE/day) for 2 years. The authors conclude: "Overall, there were no statistically significant differences among the groups in adverse-event categories after adjustment for multiple comparisons."

In a placebo-controlled crossover trial (each treatment period 4 months), Bursell et al. [3] administered 1200 mg TE/day to 36 type 1 diabetics and 9 nondiabetic subjects. The authors reported 5 mild adverse events in each (placebo and treatment) group. Standard clinical laboratory results showed that vitamin E treatment had no significant effect.

Of particular interest are the results of a double-blind study by Kim and White [7] who analysed the prothrombin time (international normalised ratio, INR) in a group of patients on

chronic warfarin therapy. The authors point out that "not 1 of the 13 patients who took vitamin E at a dose of 800 or 1200 IU/day for 1 month had an INR increase that required a change in the warfarin dose. They conclude "that if a patient receiving chronic warfarin therapy takes vitamin E in a dose as high as 1200 IU/day for 1 month, the likelihood of seeing a clinically meaningful change in the … INR is negligible".

The FSA Expert Group on Vitamin and Minerals quotes the results of the CHAOS trial by Stephens et al. [14] with 2002 patients with atherosclerosis and who had experienced one heart attack before being admitted to the study group (1035 patients were treated with vitamin E (VE), with a median follow-up time of 510 days), as support for its recommendation of a safe upper limit of 540 mg TE/day. The report also cites recent large scale clinical trials with VE supplementation, none of which have reported any adverse effects or toxicity with VE even after supplementation for a number of years at intakes which are higher than the UL decided by the SCF. For example, the Heart Protection Study [6] used 20536 high-risk adults randomised to either an antioxidant cocktail (containing 600 mg VE) or placebo per day for 5 years. The Primary Prevention Project [11] used 4495 high-risk subjects randomised to either synthetic VE (300 mg/d) or aspirin for a mean of 3.6 years in a 2×2 factorial design. The Heart Outcomes Prevention Evaluation Study [15] used 9541 high risk subjects randomised to either 400 mg/d VE, placebo or an ACE inhibitor for 4–6 years in a 2×2 factorial design.

Haemorrhagic stroke

In the alpha-tocopherol beta-carotene (ATBC) study [8] with a daily supplementation of 37 mg TE/day for 5–8 years in male smokers, an increased risk of subarachnoid haemorrhagic and a decreased risk of cerebral infarction were observed. However, the authors conclude that "the overall net effects of either supplementation on the incidence and mortality from stroke were nonsignificant". In a more detailed analysis of the data, Leppälä et al. [9] reported that these effect were restricted to hypertensive men, but that no effect on stroke was observed among normotensive men. The actual numbers of subjects who suffered from haemorrhagic stroke in the original ATBC study was remarkably low (7.8 per 10000 deaths with VE supplementation versus 5.2 per 10000 deaths without VE supplementation); thus, this may have been a chance finding which is given more credence given that this effect has not been found in any other clinical trial.

Conclusions

Based on the totality of the available evidence, a vitamin E UL of 800–1200 IU/day or 540–800 mg of tocopherol equivalents/day is considered appropriate. Since no adverse effects have been found with this dosage in various studies of good quality and of sufficient length of observation period with individuals who were considered to be at relatively high risk, application of an uncertainty factor is not justified. Furthermore and importantly, adverse effects of vitamin E have not been confirmed in patients at risk for impairment of blood coagulation. It is therefore concluded that the UL of 270 mg/d recommended by the SCF should be reconsidered in view of the present knowledge.

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