Scientific Committee on Food

Opinion
of the Scientific Committee on Food
on
the Tolerable Upper Intake Level of Vitamin κ

(expressed on 4 April 2003)

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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

All compounds with vitamin K activity contain a 2-methyl-1,4-naphthoquinone nucleus with a lipophilic side chain at position 3. More than 100 substances with vitamin K activity are known but only three are of physiological importance. Vitamin K_1 (α-phylloquinone), isolated from green plants, has a phytyl group in position 3. Vitamin K_2 (menaquinones), synthesized by bacteria, have an unsaturated multiprenyl group in this position. Of a wide range of menaquinones synthesized by bacteria, those with 7, 8 or 9 isoprenoid groups in the side chain (30 or 35 C-atoms) are most common. Menadione is a synthetic compound without a side chain, the use of which has been discontinued in dietary products and this will not be considered further.

The current consideration of a tolerable upper level for vitamin K concentrates on phylloquinone, the predominant dietary source.

2. NUTRITIONAL BACKGROUND

2.1 Sources and intakes

Vitamin K_1, or phylloquinone, is obtained from the diet whereas vitamins K_2 are also produced by the intestinal microflora (Shearer, 1992 and 1995). The extent to which vitamin K synthesis by intestinal bacteria contributes to vitamin status requires further investigation (Suttie, 1996).

The phylloquinone concentration in most foods is very low (<10 μg/100 g), and the majority of the vitamin is obtained from a few leafy green vegetables and four vegetable oils (soybean, cottonseed, canola and olive) that contain high amounts (Booth *et al.*, 1996; Fenton *et al.*, 1997). In green vegetables, vitamin K_1 is tightly bound to the thylakoid membrane of chloroplasts from where it is poorly absorbed (5-15% depending on concomitant fat intake) (Gijsbers *et al.*, 1996; Schurgers and Vermeer, 2000). The absorption of vitamins K_2, which occur mainly in cheese, curd cheese and natto, is much better and may be almost complete. Thus the nutritional importance of menaquinones is often underestimated.

Reliable measurements of phylloquinone contents in foods are now available, and data from many studies of phylloquinone intake in the United States indicate that the mean intake of younger adults (<45 years) ranges from 60 to 110 μg of phylloquinone/d. In contrast, older adults (>55 years) consume 80 to 210 μg of phylloquinone/d, attributed to their greater vegetable consumption compared to younger age groups (Booth et al., 1996). A provisional estimate of the phylloquinone intake in the UK is 68 μg/person/day, based on the food consumption data from the 2000 UK National Food Survey (MAFF, 2001). This figure is similar to earlier estimates for men and women, aged 22-54 years, of 72 μg/day and 64 μg/day respectively (Price et al., 1996). A longitudinal study of phylloquinone intakes (Bolton-Smith et al., 2000) found initial intakes of 67 and 69 μg/day for men and women respectively, aged 40-59 years in 1985. At follow-up 10 years later the intakes had fallen to 54 and 56 μg/day for men and women respectively then aged 50-69 years. For people aged 65 years and over, mean intakes for men and women were 66 and 57 μg/day respectively with considerable regional variations throughout the United Kingdom (Thane et al., 2002).

In The Netherlands, mean daily per capita intake was estimated to be up to 250 μg consequent on the relatively high intake of green vegetables. For menaquinone intake there are no population-based data available except for The Netherlands where menaquinones are estimated to form about 10% of total vitamin K intake (Schurgers et al., 1999).

Based on the average per capita food consumption in Finland (Ministry of Agriculture and Forestry, 1999; Statistics Finland, 2000), the average vitamin K intake from different foods was estimated to be 120 μg/day (Koivu-Tikkanen, 2001).

Price et al. (1996) observed no seasonal differences when phylloquinone intake was assessed during spring, summer, autumn and winter.

Data on the vitamin K intake among children are limited.

2.2   Absorption and metabolism

Under normal physiological conditions, lipid soluble K-vitamins are absorbed in cooperation with bile acids and pancreatic enzymes. The efficacy of absorption (10-90% depending on the food matrix) (Schurgers and Vermeer, 2000) can be reduced by long-chain polyunsaturated fatty acids and badly absorbed lipid-soluble substances and hydrocarbons, like mineral oils and squalene. Vitamin K_1 and K_2 are stored in the liver. The total body pool of vitamin K (1.5 μg/kg body weight) is small compared to other fat-soluble vitamins and its turnover is rapid.

Under normal conditions, 30-40% of the absorbed vitamin K is excreted via the bile into the faeces, while approximately 15% is excreted in the urine as water soluble metabolites. Alimentary deficiency, disturbance of fat absorption, increased excretion, presence of antagonists, disturbance of bile function and liver disease, lead to decreased bioavailability of vitamin K (Suttie, 1996; Elmadfa and Leitzmann, 1998).

2.3   Physiological function

The physiological activity of phylloquinone is based on its ability to change between its oxidized (quinone and 2,3-epoxide) and reduced (hydroquinone) forms.

The major role of phylloquinone is the post-translational addition of a carboxyl-group into the γ-position of glutamate residues of specific proteins. In this respect, the prime physiological relevance of phylloquinone is the synthesis of coagulation proteins (Ferland, 1998; Olson, 1999 and 2000).

Whereas the vitamin K-dependent coagulation proteins are all synthesised in the liver, vitamin K is also essential for the synthesis of a number of proteins produced in extra-hepatic tissues. Examples of the latter group of proteins include:

- the bone Gla-protein, osteocalcin, which is exclusively synthesised by osteoblasts and odontoblasts, and which is a negative regulator of bone formation;

- matrix Gla-protein (MGP), which is synthesised in most soft tissues, but predominantly in cartilage (by chondrocytes) and in vessel wall (by vascular smooth muscle cells) and which is a potent inhibitor of soft tissue calcification;

- growth arrest-specific gene 6 protein (Gas6), which is a ligand for tyrosine kinases and has strong apoptopic activity in cultured cells.

Inadequate peak mineral bone density in young adulthood is a major contributor to later disease and may be caused by a combination of genetic and nutritional factors. In addition to total energy intake, the nutrients that promote bone synthesis include calcium, vitamin C, vitamin D, and vitamin K. Vitamin K is required for the γ-carboxylation of glutamate in 2 proteins induced by the vitamin D hormone in bone. Osteocalcin is a 49-residue protein with 3 carboxyglutamic acid residues, is water soluble, adheres to the bone mineral hydroxyapatite, and is secreted by osteoblasts. Matrix carboxyglutamic acid (Gla) protein contains 79 amino acid residues of which 5 are Gla residues. It is hydrophobic, insoluble in plasma, and is associated with the matrix of cartilage and bone as well as with the tunica media of the arterial vessel wall (Olson, 2000).

Luo *et al.* (1997) demonstrated that transgenic mice, lacking the vitamin K-dependent matrix Gla protein, exhibited an excessive cartilage calcification leading to reduced growth. The most striking observation in the MGP -/- mutant, however, was excessive calcification of the large arteries leading to ruptures of the aorta before the eighth week of life in all animals.

The level of osteocalcin carboxylation has been proposed as an indicator of the nutritional state of bone with respect to vitamin K. Circulating levels of undercarboxylated osteocalcin may be a sensitive marker of vitamin K inadequacy. These levels of undercarboxylated osteocalcin have been reported to be increased both in postmenopausal women and in individuals who sustain hip fracture (Binkley and Suttie, 1995; Vermeer *et al.*, 1995; Szulc *et al.*, 1993 and 1994; Knapen *et al.*, 1998; Luukinen *et al.*, 2000).

2.4   Major criteria for assessing vitamin K status

Efforts to define the human requirement for vitamin K have been hampered by a lack of knowledge of the amount of the vitamin in various foods and by the lack of sensitive methods to assess vitamin K status (Suttie, 1992).

The major criterion for assessing the adequacy of vitamin K status in human adults is the maintenance of plasma prothrombin concentrations in the normal range (from 80 to 120 µg/mL). This classic measure of vitamin K deficiency is very insensitive but recent studies

have shown that the serum concentration of under-γ-carboxylated prothrombin (PIVKA-II), the percentage of under-γ-carboxylated osteocalcin (% ucOC) in serum and the urinary γ-carboxy-glutamic acid (Gla) excretion, respond to alterations in dietary phylloquinone. Gender and age were shown to influence both osteocalcin concentrations and Gla excretion in healthy subjects (Sokoll and Sadowski, 1996). Although there is a weak correlation between serum phylloquinone and % ucOC, it was not strong enough to have predictive values as a measure of individual vitamin K status. Because of its dependence on dietary intake within the last 24 hours, serum phylloquinone is not a meaningful indicator for nutritional status (Jakob and Elmadfa 1995). Intakes of 10 μg/day for a few weeks do not prolong the prothrombin time but put subjects at risk as assessed by other measures of vitamin K deficiency.

The acquired vitamin K deficiency produced by administration of a low dose of anticoagulant warfarin was also used to assess the relative sensitivity of various measures of vitamin K status. In subjects given 1 mg warfarin/day, Bach *et al.* (1996) noted elevated PIVKA-II concentrations but no significant decrease in urinary Gla. The most striking change was an increase in % ucOC. After a 14-day warfarin treatment, the subjects were given 1 mg phylloquinone for 7 days. At the end of this 7-day-period the % ucOC was lower than the baseline period. Various PIVKA-II measures respond to this low intake of phylloquinone and Gla excretion, which indicates that the total formation of vitamin K dependent proteins is decreased (Booth and Suttie, 1998).

It appears that phylloquinone intakes equal to the current Reference values of around 1 μg/kg body weight/day are sufficient to cover the hepatic K requirement and thus to ensure full gamma carboxylation of all coagulation factors. Since undercarboxylation of extrahepatic Gla- proteins seems to be common in the healthy adult population, the current recommended intake is probably insufficient fully to carboxylate these proteins.

2.5   Recommended intakes

The Committee made no recommendation for a PRI for vitamin K but considered that an intake of 1 μg/kg body weight/day appears to be adequate and would be provided by a normal diet (SCF 1993).

More recently recommended intakes in some countries have been determined based on effects on blood coagulation. A recommended daily dietary intake for vitamin K of 65-80 μg/day or 1 μg/kg body weight/day has been proposed (D-A-CH Referenzwerte, 2000). The US Food and Nutrition Board recently increased their recommendation to 120 μg/day for adult males and 90 μg/day for adult females (FNB, 2001). Because of the lack of specific information about the vitamin K requirement of children, reference values for them are set at about 1 μg/kg body weight (FNB, 2001; D-A-CH Referenzwerte, 2000).

2.6   Vitamin K deficiency

Clinical vitamin deficiency due to dietary inadequacy is rare or nonexistent in healthy adults. Several factors that protect adults from a lack of vitamin K include 1) widespread distribution of phylloquinone in plant and animal tissues, 2) the phylloquinone cycle, which regenerates the vitamin, and 3) the microbiological flora of the gut, which synthesizes menaquinones and can contribute to meeting the requirement for vitamin K.

Newborn infants have low vitamin K status, partly due to limited intestinal synthesis, and are at increased risk of developing haemorrhagic disease secondary to vitamin K deficiency. Vitamin K is routinely administered prophylactically to newborns in many countries.

The risk of vitamin K deficiency is increased by trauma, physical debilitation, renal insufficiency and chronic treatment with large doses of broad-spectrum antibiotics (Ansell *et al.*, 1977).

Various drugs, including the 4-hydroxy-coumarins, salicylates, certain broad-spectrum antibiotics, and vitamin A and E in pharmacologic doses, act as antagonists of vitamin K.

The principal negative effect of vitamin E 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 and 1993; Diplock *et al.*, 1998). In a review of these reports (Kappus and Diplock, 1992; Elmadfa and Leitzmann, 1998; Meydani *et al.*, 1998) the conclusion was that vitamin E at high dietary intakes affects blood coagulation if vitamin K status is inadequate. High doses of α-tocopherol equivalents affected the cyclooxygenase pathway and therefore formation of thromboxane, thus impairing the thromboxane-dependent blood coagulation, and also decreased the coagulation factors II and VII (Elmadfa and Bosse, 1985).

3. HAZARD IDENTIFICATION

3.1 Acute toxicity

Acute oral toxicity studies were carried out in rats, mice and chicks. In all three species, no deaths occurred after single doses of 25,000 mg/kg body weight phylloquinone either orally or intraperitoneally (Molitor and Robinson, 1940).

3.2 Short-term studies

No adverse effects were recorded when daily oral doses of up to 2000 mg phylloquinone/kg body weight were administered to rats for 30 days (Molitor and Robinson, 1940)

3.3 Carcinogenicity

No experimental animal studies on carcinogenicity of vitamin K have been found.

One epidemiological study indicated that there was a significant association between intramuscular injection of vitamin K and childhood cancer, especially leukaemia (Golding *et al.*, 1992). No significantly increased risk was associated with oral administration (Huysman and Sauer, 1994). Several other population studies have failed to confirm an association between vitamin K administration to children and cancer. A nested case-control study using data from a large, multicentre prospective study of 54,795 children showed no association between vitamin K administration and risk of any childhood cancer, or of all cancers combined (Klebanoff *et al.*, 1993). A study of associations between leukaemia and prenatal or neonatal administration of vitamin K did not show any increased risk in neonates receiving vitamin K i.m. (Ansell *et al.*, 1996). The latter results were confirmed in other studies (McKinney *et al.*, 1998; Parker *et al.*, 1998; Passmore *et al.*, 1998). The evidence for an

association between administration of phylloquinone to neonates and childhood cancer is therefore not convincing.

3.4 Genotoxicity

Phylloquinone was reported to reduce the mutagenicity of six heterocyclic amines in the Ames *Salmonella typhimurium* assay. There was no evidence of mutagenicity of phylloquinone in the absence of the amines (Edenharder *et al.*, 1999).

Conflicting results have been obtained in studies on the ability of phylloquinone to induce sister chromatid exchanges (SCE) in human or animal leucocytes. When 5 foetal sheep were given a dose of 1 mg phylloquinone via the femoral vein, the mean number of SCEs rose from 3.94 ($\pm$0.15) prior to injection to 5.4 ($\pm$0.23) 24 hours after injection. This increase was stated to be statistically significant (Israels *et al.*, 1987). In an *in vitro* study of the concentration response for SCE induction, foetal or adult sheep leucocytes were incubated with phylloquinone at concentrations of 0.1 nM to 1 μM. At 0.1 nM the number of SCEs was increased in foetal cells but the increase in adult cells was only observed at 10 nM and above. With human leucocytes taken from adult and placental blood, an increase in the mean number of SCEs per metaphase was reported in the presence of 1 μM phylloquinone. The SCEs rose from 3.32 $\pm$0.219 to 5.76 $\pm$ 0.219 in placental leucocytes and from 5.13 $\pm$0.273 to 7.81 $\pm$0.326 in adult cells (Israels *et al.*, 1987). Conversely, negative results were obtained when human neonates were injected with 1 mg phylloquinone i.m. No significant difference in the mean number of SCEs and chromosomal aberrations in peripheral blood lymphocytes between treated and untreated controls was observed 24 hours after injection (Cornelissen *et al.* 1991). Overall, the limited data presently available do not allow an adequate evaluation of the genotoxic potential of phylloquinone at the gene or chromosome level.

3.5 Reproductive/developmental toxicity

No data on reproductive toxicity were available.

3.6 Human data

In a study of the effect of vitamin K on bone metabolism in eight female athletes, no adverse effects were reported on administration of a supplementary 10 mg/day of phylloquinone for 1 month. In all subjects, vitamin K supplementation was associated with an increase in calcium binding capacity of osteocalcin (Craciun *et al.*, 1998).

A 3 x 15-day crossover study was conducted in groups of younger (20-40 years) and older (60-80 years) healthy adults; each group contained 9 individuals of each sex. During the three 15-day periods, the participants received a diet providing 100 μg/day phylloquinone. During two periods the diet was supplemented with broccoli (377 μg/day total phylloquinone) or phylloquinone-fortified oil (417 μg/day total phylloquinone). No adverse effects were reported (Booth *et al.*, 1999).

4. DOSE RESPONSE ASSESSMENT AND DERIVATION OF A TOLERABLE UPPER INTAKE LEVEL (UL)

There are no appropriate data from which to set a numerical upper limit for vitamin K.

5. RISK CHARACTERIZATION

In human studies of limited numbers, there is no evidence of adverse effects associated with supplementary intakes of vitamin K in the form of phylloquinone of up to 10 mg/day (more than two orders of magnitude higher than the recommended dietary intake of vitamin K) for limited periods of time. These limited data are supported by experimental animal studies in which no adverse effects were observed after daily administration of extremely high doses (2000 mg/kg body weight) for 30 days.

Because of the antagonistic interaction of phylloquinone and coumarin anticoagulant drugs, people taking these drugs should not significantly increase their phylloquinone intake by dietary change or by using dietary supplements without medical advice.

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