Vitamin K

Introduction

Vitamin K is a group of fat-soluble vitamins that are essential for biosynthesis of proteins involved in blood coagulation and metabolic pathways in bone and other tissues. This group includes two natural vitamers: vitamins K₁ (phylloquinone) and K₂ (menaquinone) (Institute of Medicine [IOM] 2001). Bacteria in the colon can convert vitamin K₁ to K₂. In addition, bacterial enzymes typically lengthen the isoprenoid side chain of vitamin K₂ to produce a range of K₂ forms. Three synthetic types of vitamin K are known: vitamins K₃, K₄, and K₅. Although the natural K₁ and all K₂ homologs have proven to be nontoxic, the synthetic K₃ (menadione), K₄, and K₅ have shown toxicity.

Vitamin K is effective in treating deficiency produced by coumarin-based drugs, such as warfarin (Coumadin) and certain other anticoagulants. The Food and Drug Administration (FDA) has not approved any form of vitamin K for the prevention or treatment osteoporosis (Kanai et al. 1997); however, vitamin K₄ has been shown to decrease the fracture rate in animals up to 87 percent. In the amount of 4 mg daily, vitamin K has been approved by the Ministry of Health in Japan since 1995 for the prevention of osteoporosis (Feskanich et al. 1999; Iwamoto et al. 1999).

Safety Considerations

No toxicity has been observed with high doses of the two natural forms of vitamin K: vitamin K₁ and vitamin K₂. Hence, no UL for these two forms has been established (IOM 2001; Expert Group on Vitamins and Minerals [EVM] 2003; Rasmussen et al. 2005).

Blood clotting studies in humans using 45 mg per day of vitamin K₂ (Ushiroyama et al. 2002) and even up to 135 mg per day (45 mg three times daily) showed no increase blood clot risk (Asakura et al. 2001).
Unlike the natural forms of vitamin K, however, the various synthetic isomers—K₃ (menadione), K₄, and K₅—are demonstrably toxic. Large doses have been shown to cause allergic reactions, hemolytic anemia, and cytotoxicity in liver cells (Higdon 2004). The FDA has banned all synthetic vitamin K products for over-the-counter sale in the U.S.

**Official Reviews**

**IOM (2001).** The IOM found no reports of adverse effects for vitamin K₁; hence, it concluded that there was no basis for a LOAEL or a NOAEL value. Lacking a LOAEL or a NOAEL, no UL value was established.

**Expert Group on Vitamins and Minerals (EVM 2003).** The UK’s EVM also cited Craciun et al. (1998) as evidence of a lack of adverse effect at 10 mg of K₁ per day. Because of the small size of that trial, the EVM selected a UF of 10 to correct for potential interindividual variation and therefore calculated a guidance level of 1 mg per day.

**European Food Safety Authority (EFSA 2006).** EFSA recognized that no adverse effects occurred in a small, short-term clinical trial of 10 mg of K₁ per day (Craciun et al. 1998). Given these findings, EFSA did not set a UL value.

**CRN Recommendations**

Vitamin K in its natural forms has an extremely low potential for toxicity, but the data are insufficient to establish just how low. The EVM’s application of a UF of 10 seems unnecessarily cautious in view of the absence of reports of adverse effects at intakes of 30 mg or more, although data to support the 30 mg value are sparse. Consequently, CRN identifies the UL for vitamin K as 10 mg per day. This value is based on the same clinical data identified by the EVM (Craciun et al. 1998) but without the tenfold UF. Dietary intake and intestinal biosynthesis are trivial in comparison with the UL of 10 mg. Because of the strong interaction of vitamin K with anticoagulant drugs, the UL does not apply to individuals taking such medications.
Quantitative Summary for Vitamin K

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<tbody>
<tr>
<td>CRN UL, supplemental intake</td>
<td>10 mg/day</td>
</tr>
<tr>
<td>IOM UL, total intake</td>
<td>Not determined</td>
</tr>
<tr>
<td>EFSA UL, total intake</td>
<td>Not determined</td>
</tr>
<tr>
<td>EC supplement maximum</td>
<td>Not determined</td>
</tr>
<tr>
<td>EVM, guidance level, supplemental intake</td>
<td>1 mg/day</td>
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References


http://lpi.oregonstate.edu/infocenter/vitamins/vitaminK/. (Updated May 2008.)


