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LA DIRECTRICE GENERALE

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OPINION

of the French Food Safety Agency (Afssa) on the assessment of the vitamin and mineral content of fortified foods and food supplements: vitamin K

On 11 September 2007, the French Food Safety Agency (Afssa) received a request from the Directorate General for Health, Directorate General for Food and Directorate General for Competition, Consumer Affairs and Fraud Control to assess the vitamin and mineral content of fortified foods and food supplements in the context of Regulation (EC) No 1925/2006 on the addition of vitamins and minerals and certain other substances to foods.

The analysis conducted by Afssa concerning vitamin K prompted the Agency, together with the French Health Products Safety Agency (Afssaps), to emphasise the risks associated with the addition of this vitamin to common foods or food supplements and to specify the scientific facts concerning the links between vitamin K and bone mineralisation.

After consulting the "Human Nutrition" Scientific Panel on 22 May 2008, Afssa has issued the following opinion:

Context:

The term "vitamin K" refers to a group of necessary cofactors for activating the proteins which play a key role in blood coagulation. These are fat-soluble substances all with the 2-methyl-1-4-naphtoquinone core. The best known forms are vitamin K_1 or phylloquinone of plant origin and vitamin K_2 or menaquinone (MKn[1]) of animal origin (bacterial).
Vitamin K_1 is featured in Annex 1 of Regulation (EC) No 1925/2006 on the addition of vitamins and minerals and certain other substances to foods, and in Annex 1 of Directive 2002/46/EC on food supplements. In France, the order of 9 May 2006 on nutrients that can be used in the manufacture of food supplements authorises the use of vitamin K_1 at the maximum daily intake level of 25µg. The vitamin K_2 group is not mentioned in these texts.

In view of the general biochemical and physiological properties of vitamin K:

The principal role of vitamin K is the gamma-carboxylation of the glutamate residues of specific proteins. It is involved in synthesising coagulation proteins: factors II, VII, IX, X and proteins C, S, Z in particular, as well as bone proteins (Vermeer et al, 1995, Bügel, 2008).

In view of the risk for the population linked to the role of vitamin K in coagulation:

In their studies geared to setting safety limits (Upper tolerable level or UL) for a list of vitamins and minerals, the Scientific Committee on Food (SCF) and the European Food Safety Authority (EFSA) have indicated, based on a limited number of human studies, that there do not seem to be any adverse effects linked to taking phylloquinone supplements of over 10mg/d for limited periods and that this data is consistent with the results of studies carried out on animals (SCF, 2003). The SCF therefore does not consider there to be any pertinent data for setting a UL for the general population. It does, however, stress the risks incurred by patients taking vitamin K supplements along with an anti-vitamin K (AVK) anticoagulant treatment.

[1] n = number of repetitions on the side chains

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In the French population, around 1% of people are undergoing anticoagulant treatment with AVK. In Opinion no. 2003-SA-0032, Afssa however recalls the importance of ensuring a stable vitamin K intake in people receiving AVK anticoagulant treatment and that, for this reason, vitamin K supplements should not be taken. A study conducted on healthy volunteers tested the effect of vitamin K intakes on AVK anticoagulant treatments (Shurgers et al., 2004). It revealed a dose-dependent effect of vitamin K on the reduction of the International Normalised Ratio, or INR[2], with a negative impact on the INR observed with a supplementary intake starting at 50µg/d of vitamin K. It was considered that, by applying a safety factor of 2, a maximum value of 25µg of vitamin K per daily ration of food supplements should limit risks for patients receiving AVK treatment. As a result, in 2004 Afssa rejected the use of high doses, even when these are labelled so as to dissuade people receiving AVK from taking these food supplements.

In view of the proof of the role vitamin K plays in bone mineralisation:

Vitamin K is essential for the γ carboxylation of glutamyl residues of bone proteins, including the Matrix-Gla-Protein (MGP) and osteocalcin (Bone Gla Protein or BGP). This process enables them to set calcium and regulate the mineralisation of bone tissue by controlling the direction of hydroxyapatite crystals and formation/resorption coupling.

Accordingly, epidemiological studies (Epidos[3], Nurses' Health Study Cohort) have found a link between the level of non carboxylated osteocalcin circulating in the blood and the risk of fracture (Vergnaud et al., 1997; Feskanich et al, 1999). Moreover, several cross-sectional studies show a link between low vitamin K_1 intakes, reduced bone mineral density and a higher risk of fracture (Booth et al, 2003) and between a low vitamin K status and lower acquisition of bone mass in children (van Summeren et al, 2008). However, this work does not eliminate the existence of confounding factors (eating habits, lifestyle, age, etc.) connected to a lower intake of vitamin K-rich foods (mainly plant-based).

Furthermore, most of the intervention studies, conducted primarily among Japanese people receiving vitamin K_2 (menaquinone), show a positive effect on bone mineral density and fracture risk. These effects are observed for very high vitamin K_2 intakes (45 mg/d) (Pearson, 2007).

Several studies have analysed the effect of vitamin K_1 on bone mineralisation (Braam et al, 2003a; Braam et al, 2003b; Bolton-Smith *et al.*, 2007; Booth *et al.*, 2008; Bügel *et al.*, 2007). Braam et al, (2003a) demonstrated that phylloquinone consumption at 1mg/d for three years reduces bone loss in postmenopausal European women. Likewise, in the study by Bolton-Smith et al (2007), a daily intake of 200 µg of vitamin K_1 for two years in elderly women increased the bone mineral content of the extremity of the radius, provided that 1g of calcium and 10 µg vitamin D were being consumed at the same time (Bolton-Smith et al, 2007). In the study by Bügel et al (2007) however, a vitamin K_1 supplement of 200 or 500 µg/d for six weeks in postmenopausal women had no effect on the bone resorption markers, even though serum concentrations of carboxylated osteocalcin increased. A randomised, double-blind study did not show any effect on bone from a 500 µg/d intake of vitamin K_1 either, in 60-80 year-old men and women over a three-year period (Booth et al, 2008). Lastly, it was found that daily 10mg supplements of vitamin K_1 in young female athletes over two years does not improve their bone status (Braam et al, 2003b).

At the present time, the results of the studies do not agree on whether or not vitamin K fortification has a beneficial effect on the general population.

Conclusion and recommendations:

Afssa does not consider there to be sufficient data at present proving a beneficial effect on the skeleton of vitamin K fortification for the general population.

Moreover, although a safety limit (upper tolerable level) cannot be defined for the general population, the high prevalence of people receiving an AVK anticoagulant treatment justifies extreme caution concerning the fortification of everyday foods with vitamin K.

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[2] This is a test that measures the coagulation time of the patient compared with that of a control value (in a healthy subject).

[3] EPIDOS: Epidemiology of osteoporosis

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As a result, Afssa is opposed to fortifying everyday foods with vitamin K, since it poses a risk that is very difficult to control in people receiving AVK.
Afssa also maintains the maximum dose of 25µg/d for food supplements, which does not appear to pose a risk for patients receiving AVK, and upholds its rejection of using higher doses, even when they are labelled so as to dissuade people receiving AVK from taking these food supplements.

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