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Nutrient Reference Values for Australia and New Zealand  
Including Recommended Dietary Intakes

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## VITAMIN K

### BACKGROUND

Vitamin K is the family name for a series of essential fat-soluble compounds needed for the chemical modification of a small group of proteins with calcium-binding properties (vitamin K dependent proteins or  $\gamma$ -carboxyglutamic acid-proteins, generally known as Gla proteins). The best-known role for vitamin K is the maintenance of normal blood coagulation. Use of anticoagulant drugs such as warfarin can affect vitamin K requirements. The vitamin K-dependent coagulation proteins that are made in the liver have both coagulant and anticoagulant properties. They include the coagulant factors II (prothrombin), VII, IX and X and the anticoagulant proteins C and S.

Vitamin K is involved in the post-translational modification of glutamate residues to  $\gamma$ -carboxyglutamate residues in the formation of the coagulation protein, prothrombin. The glutamate-containing (under-carboxylated) precursors of the vitamin K-dependent proteins are sometimes referred to as 'proteins induced by vitamin K absence' or 'PIVKA'. The glutamate precursor of prothrombin is called PIVKA-II. The vitamin K-dependent procoagulants are secreted from the liver as inactive forms. After the incorporation of Gla residues and in the presence of calcium ions they bind to the surface membrane phospholipids of platelets and endothelial cells where they form membrane-bound complexes with other cofactors. When coagulation is initiated, the inactive clotting factors are cleaved and activated.

Two other proteins containing  $\gamma$  carboxyglutamate residues are osteocalcin or bone Gla protein (with 3 Gla residues) produced by the osteoblasts and matrix Gla protein, or MGP, (with 5 Gla residues). Low vitamin K intakes are associated with undercarboxylated osteocalcin increases and have also been associated with increased rates of hip fracture in two cohort studies (Booth et al 2000, Feskanich et al 1999).

The only important molecular form of vitamin K in plants is phylloquinone (vitamin K<sub>1</sub>) but bacteria can synthesise a family of compounds called menaquinones (vitamin K<sub>2</sub>). The major dietary sources of vitamin K are green leafy vegetables such as kale, spinach, salad greens, cabbage, broccoli and brussel sprouts and certain plant oils such as soybean and canola oils (and to a lesser extent cottonseed and olive oils) and margarines and salad dressings made from them. Relatively large amounts of menaquinones can be found in some cheeses (Schurgers et al 1999).

There is little information about the bioavailability of phylloquinone from various foods. One study showed that its availability from a supplement was 25 times greater than that from spinach (Gijssbers et al 1996), although three times as much was absorbed when butter was added to the spinach. Another study showed that the availability from spinach, broccoli or romaine consumed as part of a meal was 80–84% lower than that from a supplement (Garber et al 1999). Overall, absorption from plant sources including plant oils (Booth et al 1999) seems to be no more than 20% of that from a supplement. Animal experiments have shown that high vitamin E intakes can antagonise the action of vitamin K (Rao & Mason 1975, Wooley 1945). Some effects have been seen in anticoagulated patients (Corrigan & Ulfers 1981), but no adverse effects have been shown in healthy humans.

Vitamin K deficiency causes a bleeding tendency through a lack of activity of the procoagulant proteins. A clinically significant deficiency is associated with an increase in prothrombin time (PT). Cases of dietary induced deficiency are rare, but may be associated with lipid malabsorption (Savage & Lindenbaum 1983). Experimentally induced deficiency occurred in 10 healthy subjects fed a diet containing less than 10  $\mu\text{g}$  vitamin K/day (Udall 1965). Frick et al (1967) administered a parenteral nutrient solution to a small number of neomycin-treated adults for 4 weeks and observed prolonged prothrombin times (PTs) that responded to parenteral administration of phylloquinone. Frick et al (1967) concluded that requirements were between 0.30 and 1.05  $\mu\text{g}/\text{kg}$  body weight. In more recent studies by Allison et al (1987) and Ferland et al (1993), healthy individuals eating diets containing 5–10  $\mu\text{g}/\text{day}$  for two weeks showed no change in PT.

The biologic functions of vitamin K-dependent proteins produced in other tissues, notably osteocalcin and MGP are unclear. Evidence of a possible association of suboptimal vitamin K deficiency with increased risk of adverse outcomes for bone health and bone fracture is under investigation by a number of groups but the outcomes have not been clear cut to date (Binkley & Suttie 1995, Binkley et al 2002, Braam et al 2003, Schaafsma et al 2000, Shearer 1997, Vermeer et al 1995).

Various indicators for vitamin K requirements have been used, including PT, Factor VII, plasma and serum phylloquinone, urinary  $\gamma$ -carboxyglutamyl residues, undercarboxylated prothrombin and under- $\gamma$ -carboxylated osteocalcin. Of these, only prothrombin has been associated with adverse clinical effects. Other indicators respond to dietary intake, but the physiological significance is unclear.

## RECOMMENDATIONS BY LIFE STAGE AND GENDER

<b>Infants</b>	<b>AI</b>	<b>Vitamin K</b>
0–6 months	2.0 $\mu\text{g/day}$	
7–12 months	2.5 $\mu\text{g/day}$	

**Rationale:** The AI for 0–6 months was calculated by multiplying the average intake of breast milk (0.78 L/day) by the average concentration of vitamin K in breast milk, and rounding. The figure used for breast milk was 2.5  $\mu\text{g/L}$  based on the studies of Canfield et al (1990, 1991), Greer et al (1991, 1997), Haroon et al (1982), Hogenbirk et al (1993) and Von Kries et al (1987).

The AI assumes that infants also receive prophylactic vitamin K at birth in amounts recommended in the *Joint Statement and Recommendations on Vitamin K administration to newborn infants to prevent vitamin K deficiency bleeding in infancy* from the NHMRC, Paediatric Division of the Royal Australasian College of Physicians, Royal Australian and New Zealand College of Obstetrics and Gynaecology, Royal Australian College of General Practitioners and Australian College of Midwives Inc (NHMRC et al 2000). In New Zealand, all babies receive such a supplement with parental consent.

Infant formula generally has much higher levels of phylloquinone than breast milk. Reported levels range from 50–100  $\mu\text{g/L}$  (Greer 1995, Haroon et al 1982). The AI for older infants was derived from that of younger infants on a body weight basis.

<b>Children &amp; adolescents</b>	<b>AI</b>	<b>Vitamin K</b>
<b>All</b>		
1–3 yr	25 $\mu\text{g/day}$	
4–8 yr	35 $\mu\text{g/day}$	
<b>Boys</b>		
9–13 yr	45 $\mu\text{g/day}$	
14–18 yr	55 $\mu\text{g/day}$	
<b>Girls</b>		
9–13 yr	45 $\mu\text{g/day}$	
14–18 yr	55 $\mu\text{g/day}$	

**Rationale:** There are no data on which to set an EAR for children and adolescents, so an AI has been set based on median intakes from a re-analysis of the National Nutrition Survey of Australia, 1995 using the USDA nutrient data base, and rounding up.

<b>Adults</b>	<b>AI</b>	<b>Vitamin K</b>
<b>Men</b>		
19–30 yr	70 µg/day	
31–50 yr	70 µg/day	
51–70 yr	70 µg/day	
>70 yr	70 µg/day	
<b>Women</b>		
19–30 yr	60 µg/day	
31–50 yr	60 µg/day	
51–70 yr	60 µg/day	
>70 yr	60 µg/day	

**Rationale:** There are not sufficient dose-response data to set an EAR for vitamin K in adults, so an AI has been set based on population median intakes from a reanalysis of the National Nutrition Survey of Australia, 1995, using the USDA data base. The AI is the highest median intake of any age group within the gender, rounded up. Experimental data indicate that these levels are well above the level needed to maintain a normal PT in otherwise healthy people and are in line with the intakes recommended by FAO:WHO (2001), the UK (1991) and the German/Austrian/Swiss Nutrition Societies (2002). They are, however, considerably lower than those recently recommended by the US (FNB:IOM 2001), based on median intakes in that country. Ferland et al (1993) found no difference in PT on dietary intakes of 10 µg/day or 80 µg/day in 32 subjects. Suttie et al (1998) found no change in PT during a depletion diet phase of 30–40 µg/day. Jones et al (1991) found that PT was in the normal range at a dietary intake of 40–60 µg/day and Bach et al (1996) found that PT was in the normal range in 18 people consuming about 70 µg/day in the baseline of their study. In general, changes in PT have only been seen at dietary intake levels well below 10 µg/day, although some changes in other indicators such as PIVKA II and plasma phyloquinone have been seen at intakes of 2–5 µg/day (Allison et al 1987).

<b>Pregnancy</b>	<b>AI</b>	<b>Vitamin K</b>
14–18 yr	60 µg/day	
19–30 yr	60 µg/day	
31–50 yr	60 µg/day	

**Rationale:** There are no data to suggest that the vitamin K requirement in pregnancy differs from that of the non-pregnant woman. No additional amount in pregnancy has been recommended by the FAO:WHO, the US, the UK or European countries. Thus the AI is set at the level for non-pregnant women.

<b>Lactation</b>	<b>AI</b>	<b>Vitamin K</b>
14–18 yr	60 µg/day	
19–30 yr	60 µg/day	
31–50 yr	60 µg/day	

**Rationale:** There are no data to suggest that the vitamin K requirement in lactation differs from that of the non-lactating woman. The vitamin K content of milk is relatively low and is little affected by maternal dietary intake in healthy women (Greer et al 1991). Thus the AI is set at the same level as for non-lactating women.

## UPPER LEVEL OF INTAKE - VITAMIN K

**There have been no ULs set for vitamin K.**

**Rationale:** No adverse effects have been associated with vitamin K consumption as food or supplements in humans or animals, so it is not possible to set a UL.

## REFERENCES

- Allison PM, Mumma-Schendel LL, Kindberg CG, Harms CS, Bang NU, Suttie JW. Effects of a vitamin K-deficient diet and antibiotics in normal human volunteers. *J Lab Clin Invest* 1987;110:180–8.
- Australian Bureau of Statistics: Commonwealth Department of Health and Ageing. *National Nutrition Survey. Nutrient intakes and physical measurements. Australia, 1995*. Canberra: ABS, 1998.
- Bach AU, Anderson SA, Foley AL, Williams EC, Suttie JW. Assessment of vitamin K status in human subjects administered “minidose” warfarin. *Am J Clin Nutr* 1996;64:894–902.
- Binkley NC, Krueger DC, Kawahara TN, Engelke JA, Chappell RJ, Suttie JW. A high phylloquinone intake is required to achieve maximal osteocalcin gamma-carboxylation. *Am J Clin Nutr* 2002;76:1055–60.
- Binkley NC, Suttie JW. Vitamin K nutrition and osteoporosis. *J Nutr* 1995;125:1812–21.
- Booth SL, O’Brien-Morse ME, Dallal GE, Davidson KW, Gundberg CM. Response of vitamin K status to different intakes and sources of phylloquinone-rich foods: comparison of younger and older adults. *Am J Clin Nutr* 1999a;70:368–77.
- Booth SL, Tucker KL, Chen H, Hannan MT, Gagnon DR, Cupples LA, Wilson PW, Ordovas J, Schaefer EJ, Dawson-Hughes B, Kiel DP. Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. *Am J Clin Nutr* 2000;71:1201–8.
- Braam LA, Knapen MHJ, Geusesns P, Brouns F, Hamulyak K, Gerichhaussen MJ, Vermeer C. Vitamin K1 supplementation retards bone loss in postmenopausal women between 50 and 60 years of age. *Calcified Tissue Int* 2003;73:21–6.
- Canfield LM, Hopkinson JM, Lima AF, Martin GS, Sugimoto K, Burr J, Clark L, McGee DL. Quantitation of vitamin K in human milk. *Lipids* 1990;25:406–11.
- Canfield LM, Hopkinson JM, Lima AF, Silva B, Garza C. Vitamin K in colostrum and mature human milk over the lactation period – a cross-sectional study. *Am J Clin Nutr* 1991;53:730–5.
- Corrigan JJ Jr, Ulfers LL. Effect of vitamin E on prothrombin levels in warfarin-induced vitamin K deficiency. *Am J Clin Nutr* 1981;34:1701–5.
- Department of Health. *Dietary Reference Values for food energy and nutrients for the United Kingdom. Report of the Panel on Dietary Reference Values of the Committee on Medical Aspects of Food Policy*. London: HMSO, 1991.
- Ferland G, Sadowski JA, O’Brien ME. Dietary induced subclinical vitamin K deficiency in normal human subjects. *J Clin Invest* 1993;91:1761–8.
- Feskanich D, Weber P, Willett WC, Rockett H, Booth SL, Colditz GA. Vitamin K intake and hip fractures in women: a prospective study. *Am J Clin Nutr* 1999;69:74–9.
- Food and Agricultural Organization of the United Nations: World Health Organization. *Human vitamin and mineral requirements*. Report of a joint FAO:WHO expert consultation, Bangkok, Thailand. Rome: Food and Agricultural Organization of the United Nations, 2001.
- Food and Nutrition Board: Institute of Medicine. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc*. Washington DC: National Academy Press, 2001.
- Frick PG, Riedler G, Brogli H. Dose response and minimal daily requirement for vitamin K in man. *J Appl Physiol* 1967;23:387–9.

- Garber AK, Binkley NC, Krueger DC, Suttie JW. Comparison of phyloquinone bioavailability from food sources or a supplement in human subjects. *J Nutr* 1999;129:1201–3.
- German Nutrition Society/Austrian Nutrition Society/Swiss Society for Nutrition Research and Swiss Nutrition Association. *Reference values for nutrient intake* Frankfurt/Main, Umshau/Braus: German Nutrition Society, 2002.
- Gijsbers BL, Jie KS, Vermeer C. Effect of food composition on vitamin K absorption in human volunteers. *Br J Nutr* 1996;76:223–9.
- Greer FR, Marshall S, Cherry J, Suttie JW. Vitamin K status of lactating mothers, human milk, and breast-feeding infants. *Pediatrics* 1991;88:751–6.
- Greer FR, Marshall S, Foley AL, Suttie JW. Improving the vitamin K status of breastfeeding infants with maternal vitamin K supplements. *Pediatrics* 1997;99:88–92.
- Greer FR. The importance of vitamin K as a nutrient during the first years of life. *Nutr Res* 1995;15:289–310.
- Haroon Y, Shearer MJ, Rahim S, Gunn WG, McEnery G, Barkhan P. The content of phyloquinone (vitamin K1) in human milk, cow's milk and infant formula foods determined by high-performance liquid chromatography. *J Nut* 1982;112:1105–17.
- Hogenbirk K, Peters M, Bouman P, Stuk A, Buller HA. The effect of formula versus breast feeding and exogenous vitamin K1 supplementation on circulating levels of vitamin K1 and vitamin K-dependent clotting factors in new-borns. *Eur J Pediatr* 1993;152: 72–4.
- Jones DY, Koonsvitsky BP, Ebert ML, Jones MB, Lin PY, Will BH, Suttie JW. Vitamin K status of free-living subjects consuming olestra. *Am J Clin Nutr* 1991;53:943–6.
- National Health and Medical Research Council, Paediatric Division of the Royal Australasian College of Physicians, Royal Australian and New Zealand College of Obstetrics and Gynaecology, Royal Australian College of General Practitioners and Australian College of Midwives Inc. *Joint statement and recommendations on Vitamin K administration to newborn infants to prevent vitamin K deficiency bleeding in infancy*. Canberra: Commonwealth of Australia, 2000. ISBN 0 642 45067 6.
- Rao GH, Mason KE. Antisterility and antivitamin K activity of d-alpha-tocopherol hydroquinone in the vitamin E-deficient female rat. *J Nutr* 1975;105:495–8.
- Savage D, Lindenbaum J. Clinical and experimental human vitamin K deficiency. In: Lindenbaum J, ed. *Nutrition in hematology*. New York: Churchill Livingstone, 1983. Pp 271–320.
- Schaafsma A, Muskiet FA, Storm H, Hofstede GJ, Pakan I, Van der Veer E. Vitamin D (3) and vitamin K (1) supplementation of Dutch postmenopausal women with normal and low bone mineral densities: effects on serum 25-hydroxyvitamin D and carboxylated osteocalcin. *Eur J Clin Nutr* 2000;54:626–31.
- Schurgers LJ, Geleijnse JM, Grooee DE, Pols HAP, Hofman A, Witteman JCM, Vermeer C. Nutritional intake of vitamins K1 (phyloquinone) and K2 (menaquinone) in The Netherlands. *J Nutr Environ Med* 1999;9:115–22.
- Shearer MJ. The roles of vitamin D and K in bone health and osteoporosis prevention. *Proc Nutr Soc* 1997;56:915–37.
- Suttie JW, Mummah-Schendel LL, Shah DV, Lyle BJ, Greger JL. Vitamin K deficiency from dietary vitamin K restriction in humans. *Am J Clin Nutr* 1988;47:475–80.
- Udall JA. Human sources and absorption of vitamin K in relation to anticoagulation stability. *JAMA* 1965;194:107–9.
- Vermeer C, Jie KS, Knapen MH. Role of vitamin K in bone metabolism. *Ann Rev Nutr* 1995;15:1–22.
- Von Kries R, Shearer M, McCarthy PT, Haug M, Harzer G, Gobel U. Vitamin K1 content of maternal milk: influence of the stage of lactation, lipid composition, and vitamin K1 supplements given to the mother. *Pediatr Res* 1987;22:513–7.
- Wooley DW. Some biological effects produced by -tocopherol quinone. *J Biol Chem* 1945;159:59–66.