

Vitamin K in Milk — Anlene Risk Assessment

Vitamin K Intake Recommendations

Vitamin K occurs naturally in two forms; phylloquinone (plants) and menaquinone (bacteria). There is no recommended daily intake for Vitamin K (phylloquinone) as no dose response relationship has been established¹. Vitamin K as menaquinone is synthesized in the lower bowel by bacteria. Adequate intake data is set from average dietary intakes from healthy individuals. Vitamin K deficiency occurs rarely, usually in individuals with fat malabsorption disorders. Deficiency has been induced in individuals fed less than 10µg per day¹. No upper limit of intake has been set due to the absence of adverse effects of consuming large amounts of vitamin K in healthy populations². Vitamin K was investigated for the possibility of being carcinogenic in large doses, but no relationship has ever been established.¹ These investigations mainly concerned administration of intra-muscular vitamin K for prevention of vitamin K deficiency bleeding in newborns.

Recommendations for Children (µg per day):

	1-3 yrs	4-8 yrs	9-13	14-18
US AI ¹	30	55	60	75
ESADDI (FSANZ*) ³	15			
NRV NZ ²	25	35	45	55

Recommendations for Adults (µg per day):

	Men 19 +	Women 19 +	Pregnancy	Lactation
US AI ¹	120	90	90	90
ESADDI (FSANZ*) ³	80	80	80	80
NRV NZ ²	70	60	60	60

* Estimated Safe and Adequate Daily Dietary Intake as set out in Food Standards Code 1.1 – the code is ambiguous as to the recommendations for children above the age of 3.

Anlene has vitamin K added based on the ESADDI level, 80µg per day, in the Food Standards code 1.1. Two 200ml serves of Anlene provides 80µg vitamin K.⁴

Dietary Sources of Vitamin K

As Vitamin K (phylloquinone) is a fat soluble vitamin, food sources containing fat provide higher bioavailability than those with low fat levels. Good food sources (>100µg per 100g) include green and/or leafy vegetables (broccoli, spinach, Brussels sprouts, cabbage, lettuce), soybean oil and canola oil (and their use in products such as margarine, baked goods and salad dressing). The usual vitamin K content of milk is <1µg per 100g.¹

While Anlene does not fit the criteria for a special purpose food, there are formulated meal replacements and special purpose foods that contain vitamin K. For comparison purposes the vitamin K contents per 200ml are:

	Anlene	Ensure Plus	Complan	Sustagen
Vitamin K μg per 200ml	40	24	20	25

Bioavailability of supplemental (synthetic) vitamin K is 2 to 20 times that of vitamin K from food.⁴ The bioavailability from Anlene is unknown but assumed to be higher than from food due to the addition of synthetic vitamin K.

Vitamin K Intakes

Vitamin K was not investigated in the Children's Nutrition Survey or the National Nutrition Survey hence intake in the NZ population is not known. Vitamin K is not a nutrient in the NZ Food Composition Database. European and American adult studies have shown intakes range from 61-210 μg per day with an average intake of 80 μg per day.¹

Due to the lack of toxicity for vitamin K, there is no evidence that consuming this level of vitamin K in healthy adults, or even healthy children above the age of 3, would be harmful. There is no evidence in children however, who may drink substantially more of the product than adults, that this amount of vitamin K would be beneficial. The only foreseeable problem population is illustrated below.

Vitamin K and Blood-thinning Medications

The major interaction seen with vitamin K is with the blood thinning medication warfarin. Warfarin is a prescription only medication, available in New Zealand as two trade name drugs – Coumadin (GlaxoSmithKline) and Marevan (Healthcare Logistics). Warfarin is an anti-coagulant used to prevent stroke, deep vein thrombosis and thromboembolism after myocardial infarction. Its main mode of action is as a vitamin K antagonist, inhibiting the synthesis of vitamin K dependant coagulation factors. In 2005 218,000 warfarin prescriptions were written by doctors in NZ. This is a patient-year equivalent of 46,000 people per year on warfarin (excluding those on it for short periods, and taking into account the number of prescriptions in a year).⁵

The administration of warfarin is dependant on pro-thrombin time (PT), as measured by INR (observed PT ratio). Thus dosage of the drug is individually determined by starting with a small dose and measuring the initial INR, then increasing the dose until the INR reaches the therapeutic range. The patient then requires intensive monitoring in the initial phase of starting on the drug, until an effective dose is established. The INR is affected by several factors including the vitamin K content of the diet, other medications, health conditions, temperature and alcohol use. If the INR is too low, the warfarin is not eliciting a therapeutic effect. If the INR is too high bleeding times will be longer thus increasing the risk of haemorrhage.⁶

When patients are started on warfarin they are advised to keep the vitamin K content of their diet constant, by eating the same amounts of green leafy vegetables and soy/canola oil every

day.⁷ They may however simply be told not to vary their green vegetable intake, and not be advised specifically about vitamin K at all. Three patient handouts have been identified, two given by the large pharmacy chains (variants of the Medsafe consumer data sheets) the first time a patient starts on warfarin, the other by Waitemata DHB. Both mention vitamin K as well as green leafy vegetables. If the warfarin dose is established with a constant level of vitamin K intake the INR will not be affected. The issue arises when vitamin K intakes are varied. If a patient suddenly lowers their vitamin K intake, the INR will increase, and if a patient increases their vitamin K intake the INR will decrease. Once patients are stabilized on warfarin their INR is monitored 4-8 weekly⁸.

The level at which vitamin K intake will interfere with warfarin is still debated. One study observed the effect of either a single vitamin K rich meal or a vitamin K supplement on INR.⁹ The three relevant foods studied were broccoli, spinach and curd cheese. The participants were 12 healthy volunteers aged 26-31, much younger than the expected median age for warfarin users. One participant experienced a clinically significant drop in INR that lasted 24 hours after the broccoli and spinach meals. The study concluded that one off vitamin K rich meals do not significantly affect INR, but it did not assess the effect of changing the total daily vitamin K content of the diet. The supplemental vitamin K was seen to lower the INR significantly at 150µg per day in women and 200µg per day in men. One 57kg woman had a significantly lowered INR at 100µg per day. This study is very small and the low age of the participants makes it difficult to extrapolate results to the predicted older warfarin using population.⁹

A slightly larger observational study (Franco et al) of 39 subjects, whose mean age at 57 better reflected the population on warfarin, were followed for 230 outpatient visits.¹⁰ Under-coagulation was observed in 63 visits and over-coagulation in 24 visits. Those who experienced under-coagulation (high INR) had decreased their intake of lettuce and other greens in the week prior to testing, and likewise those who experienced over-coagulation (low INR) increased their consumption of vitamin K rich greens. To further illustrate this, 12 patients were enrolled in a cross-over study where their baseline diet was either increased in vitamin K by 500% or decreased by 80%. Meals were served at the hospital to ensure compliance. INR increased progressively over a 7 day period on the vitamin K depleted diet, and decreased on day 4 on the enriched diet. The authors concluded that a change in vitamin K intake over a 4-7 day period could destabilize anti-coagulation therapy, with the vitamin K enriched diet having a more rapid effect due to it being a 500% increase compared to an 80% decrease.¹⁰

Two studies by Kurnik et al further demonstrate the interaction. They described three case studies in Israel where the patients began to take a multivitamin supplement containing 25µg vitamin K. All three had very low intakes of vitamin K and so were hypersensitive to the effects of even such a small supplemental dose. Two patients began to take a supplement and had INR decreases of 1.1 and 0.9 respectively. One patient stopped taking the supplement and had an INR increase of 10.3.¹¹ In a second study to confirm the hypersensitivity of vitamin K depleted patients on warfarin, Kurnik et al compared a group with low vitamin K and one with normal vitamin K. The depleted group were given a vitamin K containing supplement and experienced decreases in INR by a median of 0.51 and warfarin dose was raised on average 5.3%.¹²

A study by Sconce et al noted that those with a low vitamin K intake tend to have the most difficulty stabilizing INR on warfarin.¹³ Reese and colleagues then demonstrated that daily

low dose vitamin K supplementation (100µg per day) is beneficial to stabilize INR. This was closely monitored however and the warfarin dose adjusted. The study participants would then have been required to either stay on the vitamin K supplement long term, or stop the supplement and have their dose readjusted.¹⁴

A 1999 review article by Booth et al reported the 4 early studies that suggested vitamin K affected warfarin, when patients went on weight loss diets promoting high vegetable intakes.⁶ This review suggested that 25-115µg phylloquinone could induce warfarin resistance.

The use of Anlene by patients on warfarin may be expected to affect their INR. Warfarin is mainly used in older populations due to its use in secondary prevention of stroke and myocardial infarction. Older women particularly in this population are likely to be a potential target market for Anlene due to their risk of osteoporosis. Another scenario is women choosing Anlene for bone health and their partners who may also be warfarin users using the milk because it is there. Potential groups at most risk are those with a low vitamin K intake or plasma level usually, those who are unstable on warfarin and warfarin users with high milk intakes (see Appendix A for high user information).

The main issue is the sudden increase in vitamin K intake, which is not likely to be limited to one meal. For someone consuming 60µg per day to add two glasses of Anlene would increase their vitamin K intake by 140%. The 500% increase used in the Franco study seemed to affect the time taken to reduce INR – 4 days compared to 7 days with the 80% decrease. Thus an increase of 140% could reasonably be expected to have an effect on INR, after approximately 5 to 6 days. The potential consequence of the decreased INR would be that warfarin is not achieving the therapeutic range and the risk of a thrombotic event would be the same as if they were not taking medication. To incorporate Anlene into their diet safely, they would need to do this in conjunction with their GP to ensure their warfarin dose is adjusted to take into account this new vitamin K level. Once this new dose is started, the patient would need to continue their intake of Anlene at a constant level. If they were to decrease their Anlene intake they would again need to have their INR checked and warfarin readjusted. The potential consequence of then ceasing Anlene consumption and not having INR checked is that the INR may increase resulting in under-coagulation and hence possible risk of haemorrhage or prolonged bleeding times. While Anlene may actually be beneficial to the stability of anti-coagulation medication, it is imperative that the warfarin user is prompted when considering using this product, to have their INR checked and liaise with their GP. GPs also need education as to the vitamin K content of Anlene and its possible interactions with warfarin.

A possible obstacle to compliance with this advice is the cost of visiting a doctor. While some warfarin users with other health conditions will be entitled to high use benefits, and the new funding to PHOs for older adults will make doctors visits cheaper, some will inevitably find the cost a barrier. Most GP surgeries charge a minimum fee for nurse visits to collect blood, if a GP consultation is required as a result of this a fee will likely be charged.

Case reports have suggested that fish oil, vitamin E, ginkgo, garlic, ginseng and St Johns wort may also affect warfarin stability. There is limited evidence however to support this association for fish oil or vitamin E, unlike the evidence available for vitamin K.⁴

In conclusion, medical advice (see Appendix B below) and the risk assessment indicates there is a risk to warfarin users with this product.

References

1. National Academy of Sciences, Dietary Reference Intakes. National Academy Press, Washington DC, 2001, page 162-189.
2. Commonwealth Department of Health and Aging, Australia. *Ministry of Health, New Zealand and National Health and Medical Research Council, Nutrient Reference Values for Australia and New Zealand including Recommended Dietary Intakes*. May 2006, Ministry of Health New Zealand.
3. FSANZ, Australia New Zealand Food Standards Code, section 1.1. New Zealand Gazette
4. Johnson MA. *Influence of vitamin K status on anticoagulant therapy depends on vitamin K status and the source and chemical forms of vitamin K*. Nutrition Reviews 2005; 63 (3): 91-98
5. Personal Communication, Pharmac New Zealand June 2006
6. Coumadin Data Sheet, www.medsafe.govt.nz, accessed June 2006
7. Booth SL, Centurelli MA. *Vitamin K: A practical guide to the dietary management of patients on warfarin*. Nutrition Reviews 1999; 57(9): 288-96. See also Patient Handouts from Waitemata DHB and Pharmacies
8. Geevasinga N, Turner N, Mackie D. *Therapeutic monitoring of warfarin – an audit of monitoring protocols and outcomes*. NZFP 2004; 31: 307-309
9. Schurgers LJ, Shearer MJ et al. *Effect of vitamin K intake on the stability of oral anticoagulant treatment: dose response relationships in healthy subjects*. Blood 2004; 104: 2682-89
10. Franco V, Polanczyk CA, Clausell N, Rohde LE. *Role of dietary vitamin K intake in chronic oral anticoagulation: prospective evidence from observational and randomized protocols*. Am J Med 2004; 116: 651-656
11. Kurnik D, Lubetsky A, Loebstein R et al. *Multivitamin supplements may affect warfarin anticoagulation in susceptible patients*. Ann Pharmacol. 2003; 37(11): 1603-6
12. Kurnik D, Loebstein R, Rabinovitz H et al. *Over-the-counter vitamin K-1 containing multivitamin supplements disrupt warfarin anti-coagulation in vitamin K-1 depleted patients*. Thromb Haemost. 2004; 92 (5): 1018-24
13. Sconce E, Khan T et al. *Patients with unstable control have a poorer dietary intake of vitamin K compared to patients with stable control of anticoagulation*. Throm. Haemost, 2005; 93(5): 799-800
14. Reese AM, Farnett LE et al. *Low dose vitamin K to augment anticoagulation control*. Pharmacotherapy 2005; 25(12): 1746-51

Appendix A

Average daily milk consumption data from NNS for population and milk consumers (no data available for high consumers)

Males 25yrs +

Milk Type	Population Avge per day	Consumers Avge per day
Standard	174g	217g
Trim	94g	160g
Flavoured	4g	534g
Milkshakes	4g	527g

Females 25 yrs +

Milk Type	Population Avge per day	Consumers Avge per day
Standard	132g	186g
Trim	97g	157g
Flavoured	2g	303g
Milkshakes	2g	311g

Consumption average for high users (95th percentile) 720ml per day

Appendix B

Responses from Medical Professionals on the Anlene Risk:

Advisors within NZFSA were aware of what the product was and the issues surrounding the product.

Dr Donald Campbell, Medical Advisor, NZFSA: From a medical perspective there appears to be a risk here to individuals taking oral anticoagulants.

While patient and health professional information is laudable I am not convinced it is sufficient. It may reach new patients being commenced on such therapy but I wonder as the appropriateness of referring to one product or will all milks be considered as a risk? I am concerned about the larger proportion of patients who are already established on therapy. They have less contact with their medical professionals, mainly having their therapy monitored through the overall primary care team. It has to be remembered that this group of patients is predominantly elderly so possibly less likely to receive and comprehend such messages. As discussed it would be useful to canvass the views of a general practitioner and a hospital specialist for their opinions (possibly also a community pharmacist).

John Reeve, Toxicology Advisor, NZFSA: I have read the two documents regarding this issue, and searched some reliable toxicology databases that I have access to via the internet, and have the following comments:

It seems to me that while there seems no problem with anlene for healthy individuals and overdosing with vitamin K not known, there is evidence that at levels of dietary intake of vitamin K around those being considered here (as normal dietary intakes, and those from consumption of fortified anlene milk) can and do affect INR stability in patients on oral anticoagulant therapy (OAC). It is also clear that consistency of vitamin K intakes is the key to INR stability. This would suggest to me that the evidence indicates that it would be important for anyone on anticoagulant therapy to consult their doctor if they significantly change their diet with respect to vitamin K.

New patients are clearly given instruction as to what foods they need to regularly consume to ensure reasonably constant vitamin K intakes, but does this include products such as fortified milks? It would seem to me that an advertising campaign that entices these patients onto a significant dietary source of extra vitamin K is likely to lead to a significant change in their intakes without them considering the potential consequences of that change to their INR status.

I understand that anlene is also supplemented with calcium, and this is clearly also likely to be an attractive proposition to patients either suffering from, or with a family history of, osteoporosis. I understand that this would also be the older members of the population. I would suggest that unless they were advised by clear and unmissable labelling to do so, they would be unlikely to have their INR rechecked after making the change to anlene. I would think that the subsequent regular checks that I understand OAC patients undergo would be likely to pick up any significant change in vitamin K intake, but in the meantime, they could be at increased risk.

I would agree that it would seem wise to have anlene clearly labelled with the type of words that would lead OAC patients to consult their GPs if making the change to this product.

Advisors outside NZFSA were not told of the product, the medium the vitamin K was in or that NZFSA considered it a risk. The two questions asked of outside advisors were: if a food company decided to put vitamin K in a common food product that doesn't normally contain it, would this pose a risk to warfarin users? If it did pose a risk, how best should that risk be communicated to warfarin users?

1. Cardiologist, Wellington Hospital: "Yes it is a problem and a warning should be put on the product warning warfarin users not to drink it"

2. Pharmacologist, Wellington Hospital: "Yes it is a problem, GPs are not likely to ask about specific products, there should be a warning on the package"

3. GP: Based on the MedSafe datasheet for Marevan: The anticoagulant effect of the medication can be decreased by administration of vitamin K. For example if a constituent of enteral feeds. As to the effect from addition to a staple food I am not sure of the risk.

4. Senior Clinical Dietitian: Fortisip (with half the vitamin K content of Anlene) has been requested by Doctors in the hospital setting to reduce a high INR.

