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Assessment of dietary intake of vitamin K and maximum limits for vitamin K in food supplements

Opinion of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food and Environment

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Assessment of dietary intake of vitamin K and maximum limits of vitamin K in food supplements

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Assessed and approved

The opinion has been assessed by the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food and Environment (Vitenskapskomiteen for mat og miljø, VKM). Kristin Holvik (chair), Livar Frøyland, Margaretha Haugen, Sigrun Henjum, Martinus Løvik, Tonje Holte Stea, Tor A. Strand and Christine Louise Parr (external expert).

(Panel members in alphabetical order after chair of the panel)

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Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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Summary

The Norwegian Scientific Committee for Food and Environment (Vitenskapskomiteen for mat og miljø, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet; NFSA), evaluated the intake of vitamin K in the diet. VKM has also assessed the consequences of establishing maximum limits for vitamin K in food supplements at 100, 200, 300, 600 or 800 µg/day. The former maximum limit for vitamin K of 200 µg/day in food supplements was repealed 30 May 2017.

Vitamin K is a fat-soluble vitamin required for the carboxylation of glutamic acid residues in proteins that regulate blood coagulation and bone metabolism. The naturally occurring forms of vitamin K present in food and supplements are phyloquinone (vitamin K1) mainly produced by plants, and a range of menaquinones (vitamin K2) mainly produced by bacteria. The chemical structure of vitamin K is characterised by a methylated naphthoquinone ring structure assumed to be responsible for its function, in addition to a side chain which differs in length and degree of saturation. Due to the varying side chains, the different forms of vitamin K are thought to behave differently with regard to absorption, metabolism, bioavailability and thereby also toxic potential.

Dark green leafy vegetables are rich sources of phyloquinone. Meat and liver products provide menaquinone-4, the most common menaquinone in Western diets, while other menaquinones are found in fermented foods and cheese.

An Adequate Intake (AI) of phyloquinone of 1 µg/kg body weight per day was set by the Scientific Committee on Food (SCF) in 1993 and maintained by the European Food Safety Authority (EFSA) in 2017. No dietary reference values (DRVs) have been established for menaquinones due to insufficient evidence. Furthermore, no tolerable upper intake levels (ULs) have been established for any form of vitamin K due to insufficient evidence, but previous reports stated that no adverse effects associated with vitamin K consumption from food or supplements had been reported in humans or animals. In 2003, the UK Expert Group on Vitamins and Minerals (EVM) proposed a guidance level (GL) for safe upper intake of supplemental phyloquinone of 1 mg/day in adults. The GL was set by applying an uncertainty factor of 10 for inter-individual variation to the supplemental dose of 10 mg/day that had been consumed by eight female athletes (age 20-44) for 30 days with no reported adverse effects. The UK expert group emphasised that GLs had been derived from limited data and were less secure than safe upper levels. This GL was supported by a double-blind randomised study cited in the Nordic Nutrition Recommendations (2012), in which 440 postmenopausal women with osteopenia received a daily supplement of 5 mg phyloquinone or placebo for up to four years with no difference in adverse events between the randomised groups.

Corresponding GLs for children and adolescents have been derived by adjusting for reference body weights^{0.75} by Rasmussen et al. (2006).

The distribution of intakes of vitamin K across age groups in Norway is not known, since food composition data is not available. However, habitual intakes in a representative sample of middle-aged and older adults in Western Norway were assessed in the population-based Hordaland Health Study 1997-2000, and revealed higher intakes than those estimated from dietary surveys in the other Nordic countries. Due to lack of representative estimates of vitamin K intakes in the Norwegian population, information on vitamin K intakes from other Nordic countries is included in the current opinion. This includes the distribution of vitamin K intakes in Sweden and Finland reported by EFSA, and the distribution of vitamin K intakes in Denmark, assessed by the Technical University of Denmark (DTU). In middle-aged and older Western Norwegians participating in the Hordaland Health Study 1997-2000, estimated mean intakes of total vitamin K (denoting the sum of K1+K2) ranged from 109 to 148 µg/day in four groups based on age and gender, while the 95-percentiles ranged from 261 to 329 µg/day. Average intakes of total vitamin K in the other Nordic countries are in the magnitude of 100 µg/day in adults, while 95-percentiles in adults are in the magnitude of 200 µg/day.

To illustrate the consequences of establishing maximum limits for vitamin K at 100, 200, 300, 600 or 800 µg/day in food supplements, VKM has compared these levels to the age-specific GLs for supplemental phylloquinone proposed by EVM (2003). The GLs are: 1000 µg/day for adults, 870 µg/day at age 15-17 years, 670 µg/day at age 11-14 years, 500 µg/day at age 7-10 years, 370 µg/day at age 4-6 years and 270 µg/day at age 1-3 years.

VKM concludes that:

- In adults and adolescents 15-17 years old, maximum limits of 100, 200, 300, 600 and 800 µg/day are below GL.
- In adolescents 11-14 years old, maximum limits of 100, 200, 300 and 600 µg/day are below GL while the maximum limit of 800 µg exceeds GL.
- In children 4-10 years old, maximum limits of 100, 200 and 300 µg/day are below GL while maximum limits of 600 µg/day and 800 µg/day exceeds GL.
- In children 1-3 years old, maximum limits of 100 µg/day and 200 µg/day are below GL while maximum limits of 300, 600 and 800 µg/day exceeds GL.

VKM notes that the current conclusions apply to phylloquinone (vitamin K1) only, while there is insufficient evidence to appraise potential health consequences of maximum limits of menaquinones (vitamin K2).

VKM emphasises that the current assessment of maximum limits for vitamin K in food supplements is merely based on published reports concerning upper levels from the IOM (2001, USA), SCF (2003, EU), EVM (2003, UK) and NNR (2012, Nordic countries). VKM has not conducted any systematic review of the literature for the current opinion, as this was outside the scope of the terms of reference from NFSA.

Key words: VKM, risk assessment, Norwegian Scientific Committee for Food and Environment, vitamin K, phylloquinone, menaquinones, food supplements, safe upper level, guidance level, exposure.

Sammendrag på norsk

Vitenskapskomiteen for mat og miljø har vurdert inntaket av vitamin K i befolkningen på oppdrag fra Mattilsynet. VKM har også gjort scenarioberegninger for å illustrere konsekvensene av å fastsette maksimumsgrensene for vitamin K i kosttilskudd til 100, 200, 300, 600 eller 800 µg/dag. Den tidligere maksimumsgrensen for vitamin K var på 200 µg per døgndose. Den ble opphevet 30. mai 2017.

Vitamin K er et fettløselig vitamin som er nødvendig for karboksylering av glutaminsyre i proteiner som regulerer blodkoagulering og benvevsomsetning. De naturlige formene av vitamin K som finnes i mat og kosttilskudd er fyllokinon (vitamin K1) som dannes av planter, og en rekke menakinoner (vitamin K2) som produseres av bakterier. Den kjemiske strukturen til vitamin K kjennetegnes ved en metylert naftokinonringstruktur som antas å være ansvarlig for vitaminets funksjon, i tillegg til en sidekjede som varierer i lengde og metningsgrad mellom de ulike former for vitamin K. På grunn av forskjeller i sidekjeden antas de ulike formene å variere i absorpsjon, omsetning og biotilgjengelighet, og dermed å ha ulikt potensiale for toksisitet.

Mørkegrønne bladgrønnsaker er gode kilder til fyllokinon. Kjøtt- og leverprodukter er kilder til menakinon-4, som er det vanligst forekommende menakinonet i vestlig kosthold. Fermenterte matvarer og ost er kilder til andre menakinoner.

Scientific Committee on Food (SCF) fastsatte i 1993 et «Adequate Intake» (AI) for fyllokinon på 1 µg/kg kroppsvekt per dag. Dette ble videreført av European Food Safety Authority (EFSA) i 2017. På grunn av utilstrekkelig kunnskapsgrunnlag, finnes det ikke et anbefalt inntak for menakinoner. På grunn av utilstrekkelig kunnskapsgrunnlag har det heller ikke blitt fastsatt et tolerabelt øvre inntaksnivå (UL) for verken fyllokinon eller menakinoner, men ifølge tidligere rapporter har det ikke blitt observert negative helseeffekter av inntak av vitamin K fra mat eller kosttilskudd hos mennesker eller dyr. I 2003 lanserte "Expert Group on Vitamins and Minerals" (EVM) i Storbritannia et "guidance level" (GL) på 1 mg/dag for voksne, som et veiledende nivå for trygt øvre inntak av tilskudd av fyllokinon. GL ble fastsatt ved å ta utgangspunkt i en kosttilskuddsdose på 10 mg/dag som hadde blitt brukt av åtte kvinnelige toppidrettsutøvere (alder 20-44 år) i 30 dager uten at negative helseeffekter var rapportert, og dividere med en usikkerhetsfaktor på 10 for interindividuell variasjon. Ekspertgruppen fra Storbritannia presiserte at GL er avledet fra et svært begrenset datagrunnlag og at det derfor hefter større usikkerhet ved GL enn andre grenseverdier for øvre inntak som UL. GL fra Storbritannia ble imidlertid støttet av en randomisert dobbelblindet studie gjengitt i nordiske næringsstoffanbefalinger fra 2012. I denne studien fikk 440 postmenopausale kvinner med osteopeni et daglig tilskudd med 5 mg fyllokinon eller placebo i opptil fire år uten at det ble observert forskjeller i negative helseeffekter mellom gruppene.

GL for barn og unge i ulike aldersgrupper har senere blitt utledet av Rasmussen et al. (2006) ved å justere 1 mg/dag for voksne for standard kroppsvekt^{0.75}.

På grunn av manglende matvaredata, er inntaket av vitamin K i alle aldersgrupper i Norge ikke kjent. I den befolkningsbaserte Helseundersøkelsen i Hordaland 1997-2000 kartla man imidlertid inntaket av vitamin K i et representativt utvalg av middelaldrende og eldre vestlendinger. Resultatet viste et høyere inntak enn estimert daglig inntak fra andre nordiske land. I denne VKM-uttalelsen presenteres inntaksdata for vitamin K i Sverige og Finland, gjengitt i EFSA's rapport fra 2017, samt inntaksdata fra Danmark som er gjort tilgjengelig av Danmarks Tekniske Universitet (DTU). I Helseundersøkelsen i Hordaland 1997-2000 varierte beregnet gjennomsnittlig inntak av total vitamin K (summen av K1+K2) mellom 109 og 148 µg/dag i fire grupper basert på kjønn og alder, mens 95-percentilene varierte mellom 261 og 329 µg/dag. Gjennomsnittlige inntak av total vitamin K i de andre nordiske land er i størrelsesorden 100 µg/dag for voksne, mens 95-percentilen for voksne er opptil 200 µg/dag.

For å illustrere konsekvensene av å fastsette maksimumsgrensene for vitamin K i kosttilskudd til henholdsvis 100, 200, 300, 600 eller 800 µg/dag, har VKM sammenliknet disse alternative maksimumsgrensene med aldersspesifikke GL for fyllokinon fra kosttilskudd basert på rapporten fra EVM (2003). GL-verdiene er: 1000 µg/dag for voksne, 870 µg/dag ved alder 15-17 år, 670 µg/dag ved alder 11-14 år, 500 µg/dag ved alder 7-10 år, 370 µg/dag ved alder 4-6 år og 270 µg/dag ved alder 1-3 år.

VKM konkluderer at:

- For voksne og ungdom 15-17 år vil maksimumsgrensene på 100, 200, 300, 600 og 800 µg/dag ligge under GL.
- For ungdom 11-14 år vil maksimumsgrensene på 100, 200, 300 og 600 µg/dag ligge under GL, mens maksimumsgrensen på 800 µg/dag vil overskride GL.
- For barn 4-10 år vil maksimumsgrensene på 100, 200 og 300 µg/dag ligge under GL, mens maksimumsgrensene på 600 µg/dag og 800 µg/dag vil overskride GL.
- For barn 1-3 år vil maksimumsgrensene på 100 µg/dag og 200 µg/dag ligge under GL, mens maksimumsgrensene på 300, 600 og 800 µg/dag vil overskride GL.

VKM bemerker at konklusjonene kun gjelder for fyllokinon (vitamin K1). Det er utilstrekkelig kunnskapsgrunnlag for å vurdere mulige helsekonsekvenser av maksimumsgrenser for menakinoner (vitamin K2).

VKM presiserer at denne vurderingen av maksimumsgrenser for vitamin K i kosttilskudd er basert på publiserte rapporter om øvre inntaksnivåer fra IOM (2000, USA), SCF (2003, EU), EVM (2003, Storbritannia) og NNR (2012, de nordiske landene). Ettersom mandatet i bestillingen fra Mattilsynet var å vurdere inntaket av vitamin K basert på allerede eksisterende rapporter, har VKM for denne uttalelsen ikke gjennomført et eget systematisk litteratursøk for å vurdere det samlede kunnskapsgrunnlaget.

Nøkkelord: VKM, risikovurdering, Vitenskapskomiteen for mat og miljø, vitamin K, fyllokinon, menakinoner, kosttilskudd, eksponering.

Abbreviations and glossary

Abbreviations

AI	– adequate intake
AR	– average requirement
bw	– body weight
DRI	– dietary reference intake
DRV	– dietary reference value
DTU	– Technical University of Denmark
EAR	– estimated average requirement (IOM)
EFSA	– European Food Safety Authority
EVM	– Expert group on vitamins and minerals of the Food Standard Agency, UK
FFQ	– Food frequency questionnaire
GL	– guidance level (for safe upper intake)
GLA	– glutamate
HPLC	– high performance liquid chromatography
IOM	– Institute of Medicine, USA
LOAEL	– lowest observed adverse effect level
NFSA	– Norwegian Food Safety Authority [<i>Norw.</i> : Mattilsynet]
NHANES	– National Health and Nutrition Examination Survey
NNR	– Nordic Nutrition Recommendations
NOAEL	– no observed adverse effect level
PRI	– population reference intake
RCT	– randomised controlled trial
RDA	– recommended dietary allowances
RI	– recommended intake
SAE	– serious adverse events
SCF	– Scientific Committee for Food
SD	– standard deviation
SUL	– safe upper intake level
UF	– uncertainty factor
UL	– tolerable upper intake level
USDA	– United States Department of Agriculture
VKM	– Norwegian Scientific Committee for Food and Environment [<i>Norw.</i> : Vitenskapskomiteen for mat og miljø]

Glossary

Percentile is a statistical measure indicating the value below which a given percentage of the observations fall. E.g. the 95-percentile is the value (or score) below which 95 percent of the observations are found.

P5, P25, P50, P75 or P95-exposure is the calculated exposure at the 5, 25, 50, 75 or 95-percentile.

EFSA - Dietary Reference Values (DRVs) (EFSA, 2010)

Average Requirement (AR) is the level of intake of a defined group of individuals estimated to satisfy the physiological requirement of metabolic demand, as defined by a the specific criterion for adequacy for the nutrient, in half of the healthy individuals in a life stage or sex group, on the assumption that the supply of other nutrients and energy is adequate.

If an AR cannot be determined than an Adequate Intake is used.

Adequate Intake (AI) is defined as the average (median) daily level of intake based on observed, or experimentally determined approximations or estimates of a nutrient intake, by a group (or groups) of apparently healthy people, and therefore assumed to be adequate. The practical implication of an AI is similar to that of a population reference intake, i.e. to describe the level of intake that is considered adequate for health reasons. The terminological distinction relates to the different ways in which these values are derived and to the resultant difference in the "firmness" of the value.

Population Reference Intake (PRI) is derived from AR of a defined group of individuals in an attempt to take into account the variation of requirements between individuals.

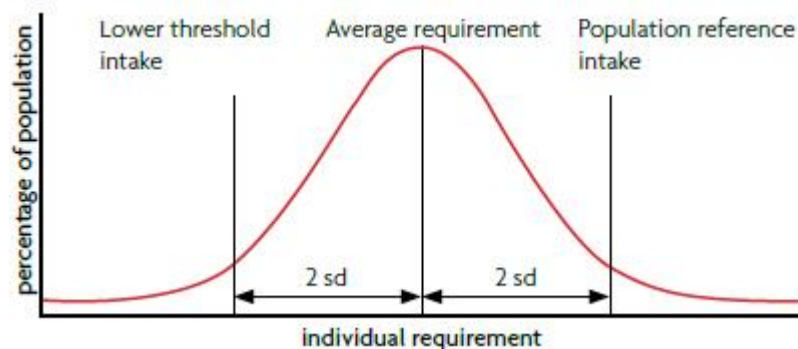


Figure 1: Population reference intake (PRI and average requirements (AR), if the requirement has a normal distribution and the inter-individual variation is known (EFSA, 2010).

Lower Threshold Intake (LTI) is the lowest estimate of requirement from the normal distribution curve, and is generally calculated on the basis of the AR minus twice its standard deviation (SD). This will meet the requirement of only 2.5% of the individuals in the population.

Tolerable Upper Intake Level (UL) is the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans.

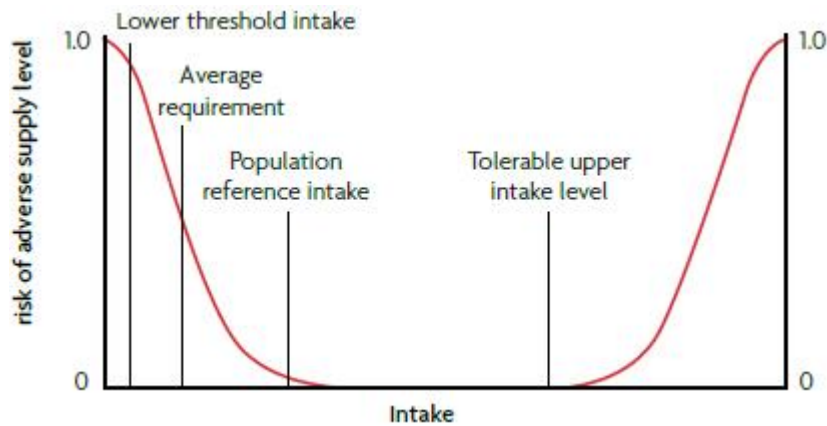


Figure 2: Relationship between individual intake and risk of adverse effects due to insufficient or excessive intake using EFSA terminology.

IOM - Dietary Reference Intakes (DRIs) (IOM, 2000)

Estimated Average Requirement (EAR) is a nutrient intake value that is estimated to meet the requirement of half the healthy individuals in a life stage and gender group.

Recommended Dietary Allowances (RDA) is the dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular life stage and gender group. $RDA = EAR + 2 SD_{EAR}$ or if insufficient data to calculate SD a factor of 1.2 is used to calculate RDA; $RDA = 1.2 * EAR$.

Adequate Intake (AI) is the recommended intake value based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of healthy people that are assumed to be adequate – used when an RDA cannot be determined.

Tolerable Upper Intake Level (UL) is the highest level of nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population.

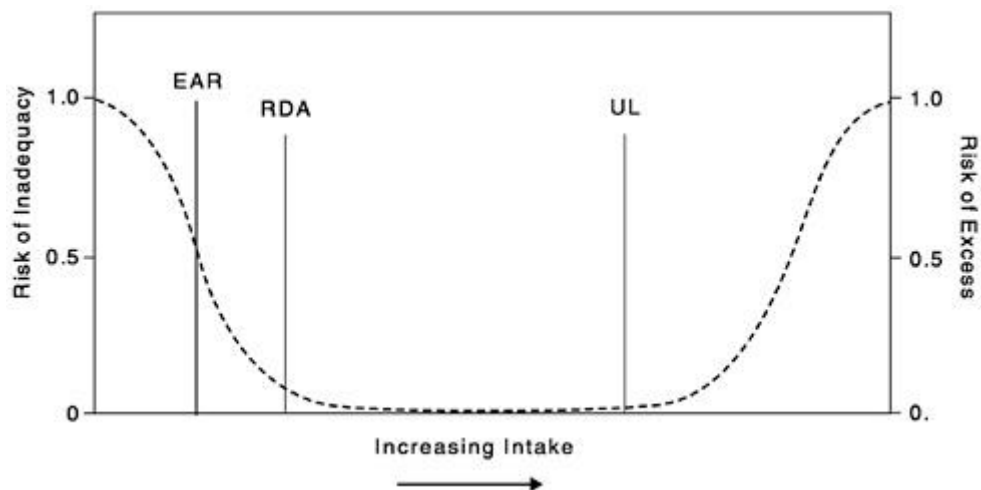


Figure 3: Dietary reference intakes using IOM terminology.

NNR -Recommended Intake (NNR Project Group, 2012)

Average Requirement (AR) is defined as the lowest long-term intake level of a nutrient that will maintain a defined level of nutritional status in an individual i.e. the level of a nutrient that is sufficient to cover the requirement for half of a defined group of individuals provided that there is a normal distribution of the requirement.

$$AR_{NNR} = EAR_{IOM} = AR_{EFSA}$$

Recommended Intake (RI) is defined as the amount of a nutrient that meets the known requirement and maintains good nutritional status among practically all healthy individuals in a particular life stage or gender group. $RI = AR + 2SD_{AR}$.

$$RI_{NNR} = RDA_{IOM} = PRI_{EFSA}$$

Upper Intake Level (UL) is defined as the maximum level of long-term (months or years) daily nutrient intake that is unlikely to pose a risk of adverse health effects in humans.

$$UL_{NNR} = UL_{IOM} = UL_{EFSA}$$

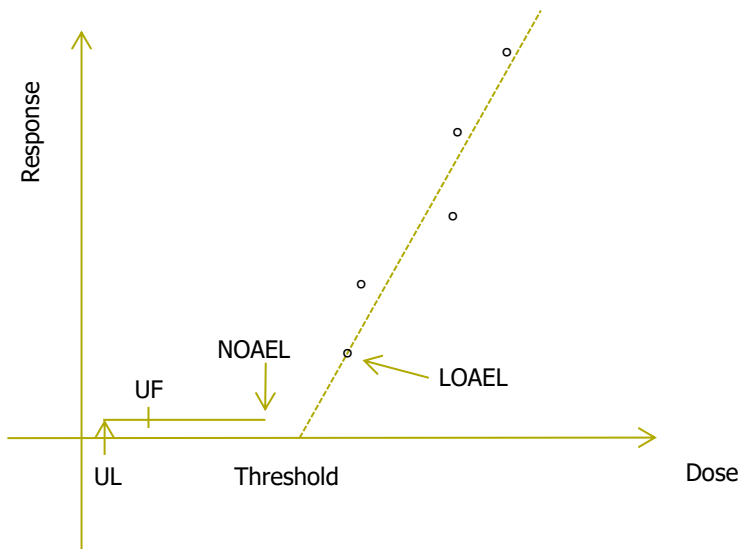


Figure 4: Derivation of Upper Intake Level (UL)
 UF: Uncertainty factor

Expert group on vitamins and minerals (EVM), UK (EVM, 2003)

Safe Upper Intake Level (SUL): EVM used SUL instead of UL and defined SUL as the intake that can be consumed daily over a lifetime without significant risk to health on the basis of available evidence. The setting of these levels provided a framework within which the consumer could make an informed decision about intake, having confidence that harm should not ensue. The levels so set will therefore tend to be conservative.

Guidance Level (GL): For vitamins and minerals where a SUL could not be established due to insufficient data, EVM provided GL as an approximate indication of levels that would not be expected to cause adverse effects. As with SULs, the GLs are intended to represent the doses of vitamins and minerals that susceptible individuals could take daily on a life-long basis, without medical supervision. The EVM emphasised, however, that GLs should not be used as SULs, as they have been derived from limited data and are less secure than SULs.

Background as provided by the Norwegian Food Safety Authority

Directive 2002/46/EC on food supplements was implemented into Norwegian law in 2004 in Regulation 20 May 2004 No. 755 on food supplements. Pursuant to Directive 2002/46/EC, common maximum and minimum levels of vitamins and minerals in food supplements shall be set in the EU. The European Commission started to establish common limits in 2006, but the work was temporarily put on standstill in 2009. The time frame for the further work is not known.

National maximum limits for vitamins and minerals were established in the former vitamin and mineral supplements regulation from 1986 and were continued in the 2004 regulation.

The national maximum and minimum limits in the food supplement regulation were established a long time before the food supplement directive was adopted, and the limits were consequently not established in accordance with the criteria for limits set in the food supplement directive. Maximum limits for vitamins and minerals which were not already revised according to the criteria in article 5 in the food supplement directive, were therefore repealed from 30 May 2017.

Maximum limits for levels of vitamins and minerals in food supplements shall be set on basis of the following criteria, pursuant to article 5 in Directive 2002/46/EC:

- Upper safe levels of vitamins and minerals established by scientific risk assessment based on generally accepted scientific data, taking into account, as appropriate, the varying degrees of sensitivity of different consumer groups
- Intake of vitamins and minerals from other dietary sources

When the maximum levels are set, due account should also be taken of reference intakes of vitamins and minerals for the population.

Pending establishment of common maximums limits in the EU, the Norwegian Food Safety Authority is evaluating the national maximum limits for vitamins and minerals in food supplements.

Norwegian authorities will as soon as possible, when it exists a scientific basis, and pending establishment of common maximums limits in the EU, establish new national maximum limits for those vitamins and minerals where limits were repealed 30 May 2017.

Assessment of vitamin K

The Norwegian Food Safety Authority will consider establishing a new national maximum limit for vitamin K in the food supplement regulation.

The former maximum limit for vitamin K was 200 µg per daily dose, but was repealed from 30 May 2017. The minimum limit and permitted vitamin K substances that may be used in the manufacture of food supplements, are listed in annex 1 and annex 2 in the food supplement regulation.

Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA, Mattilsynet) requests the Norwegian Scientific Committee for Food and Environment (VKM) to assess the intake of vitamin K from the diet, in all age groups in the population above 1 year.

As there is no data on vitamin K in the Norwegian food composition data base (KBS), VKM is requested to evaluate if other relevant intake data can be used - included Danish intake data estimated by the National Food Institute in Denmark (DTU) and the EFSA Scientific Opinion on Dietary reference values for vitamin K (2017).

VKM is also requested to evaluate the consequences of establishing a maximum limit for vitamin K in food supplements of 100, 200, 300, 600 or 800 µg per daily dose, and to evaluate these scenarios against existing tolerable upper intake levels.

1 Introduction

Vitamin K is an essential fat-soluble vitamin required for the carboxylation of glutamic acid residues in proteins that regulate blood coagulation, bone metabolism, and vascular biology (Card et al., 2014). Its name is derived from the German and Scandinavian terms for “coagulation vitamin”, after the discovery in the 1930s of a factor present in e.g. hog-liver and hemp seed with the ability to reverse deficient blood clotting in chicks (Dam, 1935). Vitamin K is a collective term for related compounds that are characterised by a methylated naphthoquinone ring structure (3-substituted 2-methyl-1,4-naphthoquinone) and a lipophilic side chain at position 3 that varies in length and saturation (Vermeer and Schurgers, 2000). While there are also synthetic analogues of vitamin K (such as menadione, often called vitamin K3), the current opinion is limited to discuss naturally occurring vitamin K present in food and supplements. Vitamin K1 designates the plant-derived phyloquinone while vitamin K2 designates the group of menaquinones produced mainly by bacteria. Phyloquinone and menaquinones differ in length and degree of saturation of their side chain. While the different forms of vitamin K are assumed to have the same mechanism of action since the naphthoquinone is considered the functional group, they are assumed to differ in absorption, transport, tissue distribution and bioavailability. Vitamin K acts as a cofactor for an enzyme that carboxylates glutamic acid residues to glutamate (GLA) in vitamin K-dependent proteins, thus enabling these proteins to bind calcium. Well-known examples are prothrombin and other coagulation factors, in addition to osteocalcin (bone GLA). Symptoms of vitamin K deficiency are related to reduced activity of these proteins, such as bleeding and impaired bone mineralisation. Warfarin is used as an anticoagulant drug based on its vitamin K-antagonistic action.

According to the USDA Food Composition Database (<https://www.ars.usda.gov>), Brassica and dark green leafy vegetables (kale, broccoli, Brussels sprouts, spinach, greens and leaves of e.g. turnip, coriander, collards, chicory) and plant oils of canola and soybean have high concentrations of phyloquinone, with amounts of 100-800 µg per 100 g food. Meat and liver products are rich sources of menaquinone-4, which is the most common menaquinone in Western diets, while other menaquinones are predominantly found in fermented foods and cheese (Schurgers and Vermeer, 2000; Vermeer and Schurgers, 2000).

Norwegian food composition data on vitamin K is currently not available, and little is known about habitual dietary intake of vitamin K in Norway. Average dietary intakes of ‘total vitamin K’ estimated by the European Food Safety Authority (EFSA) for nine EU countries ranged between 72 and 196 µg/day in adults, with large uncertainties (EFSA, 2017). In the context of the EFSA report and the current opinion, the term ‘total vitamin K’ refers to the sum of vitamin K1 and vitamin K2. In practice, however, as discussed by EFSA (2017), the contributions of vitamin K1 and vitamin K2 to ‘total vitamin K’ in dietary surveys are highly variable, depending on the availability of food composition data in the different countries.

2 Recommendations and tolerable upper intake levels

2.1 Recommendations

2.1.1 Nordic Nutrition Recommendations (2012) and European Food Safety Authority (2017)

In the fourth edition of the Nordic Nutrition Recommendations (NNR Project group, 2004), a provisional recommended intake of 1 µg/kg body weight per day of phylloquinone was set for all age groups. This corresponded to the Adequate Intake level (AI) for phylloquinone previously proposed by the former Scientific Committee on Food (SCF, 1993) (see below). This provisional recommended intake level was maintained in the fifth edition of the Nordic Nutrition Recommendations (NNR Project Group, 2012).

In 2017, EFSA adopted Dietary Reference Values (DRVs) for vitamin K (EFSA, 2017). For that opinion, EFSA reviewed recent literature on both phylloquinone and menaquinones with the aim of updating the DRVs set by the SCF (1993). The SCF had proposed an AI level for phylloquinone of 1 µg/kg body weight per day, based on an intake which appeared adequate to prevent vitamin K deficiency in healthy subjects and would be provided by a normal mixed diet (Suttie et al., 1988 cited in SCF, 1993). EFSA concluded that the uncertainties pointed out by the SCF (1993) had not been resolved, and that there was no scientific evidence to update the previous reference value. Furthermore, EFSA reported that there was insufficient data for deriving Average Requirements (ARs) or Population Reference Intakes (PRIs) for vitamin K. AIs were set for phylloquinone, but not menaquinones due to limited scientific evidence. Concerning phylloquinone, EFSA stated that "there is no indication that 1 µg/kg body weight per day phylloquinone would be associated with a risk of deficiency in the general population and is above the intake at which an increase in prothrombin time has been observed in healthy subjects". Therefore, an intake of 1 µg/kg body weight per day was maintained as an AI, applying to all age groups. The AIs for age groups based on reference body weights are presented in Table 2.1.1-1.

Table 2.1.1-1 Adequate Intakes for vitamin K1 (phylloquinone) from EFSA (2017) based on an AI of 1 µg/kg body weight per day and reference body weights. Rounded values for both sexes combined.

Age	µg/day
1-3 years	12
4-6 years	20
7-10	30
11-14 years	45
15-17 years	65
≥18 years*	70

*Including pregnancy and lactation.

2.1.2 Institute of Medicine (2001), USA and Canada

The Institute of Medicine (IOM) set AI levels for vitamin K in 2001 (IOM, 2001; Trumbo et al., 2001). It was not explicitly stated whether these AI levels applied to total vitamin K or to phylloquinone only.

For children and adolescents 1 through 18 years, no data were found on which to base an Estimated Average Requirement (EAR) for vitamin K. Therefore, AIs were set on the basis of the highest median intake for each age group reported by the third US National Health and Nutrition Examination Survey (NHANES III) and rounding.

For adults aged 19 years and older, the IOM noted the following:

“Clinically significant vitamin K deficiency is extremely rare in the general population, with cases being limited to individuals with malabsorption syndromes or those treated with drugs known to interfere with vitamin K metabolism. The recent development of indicators sensitive to vitamin K intake, though useful to describe relative diet-induced changes in vitamin K status, were not used for establishing an EAR because of the uncertainty surrounding their true physiological significance and the lack of sufficient dose-response data.”

Therefore, the AI for adults was based on reported vitamin K dietary intakes in apparently healthy population groups. A review by Booth and Suttie (1998) reported that intakes of phylloquinone ranged from 61 to 210 µg/day with average intakes of approximately 80 µg/day for adults <45 years and approximately 150 µg/day for adults >55 years (Booth and Suttie, 1998). NHANES III data indicated that median vitamin K intakes of adults varied between 82 and 117 µg/day. Based on these results, an AI of 120 µg/day was set for men and 90 µg/day for women. For pregnant and lactating women, AIs were based on median NHANES III intake estimates of non-pregnant women. The resulting AIs for vitamin K in all age groups, 1 year and older, are presented in Table 2.1.2-1.

Table 2.1.2-1 Adequate Intakes ($\mu\text{g}/\text{day}$) for vitamin K in sex and age groups according to IOM (2001).

Age	Males $\mu\text{g}/\text{day}$	Females $\mu\text{g}/\text{day}$
1-3 years	30	30
4-8 years	55	55
9-13 years	60	60
14-18 years*	75	75
≥ 19 years*	120	90

*Including pregnancy and lactation.

2.2 Tolerable upper intake levels

2.2.1 Institute of Medicine (IOM, 2001), USA

Hazard identification: The IOM considered that:

- No adverse effects associated with vitamin K consumption from food or supplements had been reported in humans or animals.
- A literature search revealed no evidence of toxicity associated with the intake of either the phyloquinone or menaquinone forms of vitamin K.
- Although a study of limited relevance had shown an association between intramuscularly administered vitamin K in neonates and childhood cancer, particularly leukemia (Golding et al., 1992, cited in IOM 2001), evidence from numerous later population studies failed to confirm an association between vitamin K and cancer. Moreover, in the early study, no increased risk was observed in children who had been given oral vitamin K.
- Data from animal models had shown no toxicity of vitamin K. No adverse effects were reported with administration of up to 25 g/kg of phyloquinone either parenterally or orally to laboratory animals.

Dose-response assessment: The IOM considered that data on adverse effects from high vitamin K intakes were not sufficient for a quantitative risk assessment.

Intake assessment: Results from NHANES III showed that 340 μg vitamin K/day was the highest reported intake from food, and 367 μg vitamin K/day was the highest reported intake from food and supplements combined among women aged 19 through 30 years.

Risk characterisation: The IOM stated that no adverse effects had been reported with high intakes of vitamin K.

Derivation of UL: The IOM concluded that since no adverse effects associated with vitamin K intake from food or supplements had been reported in humans or animals, a quantitative risk assessment could not be performed, and a tolerable upper intake level (UL) could not be derived for vitamin K.

Table 2.2.1-1 Tolerable upper intake levels (ULs) for vitamin K by the IOM (2001).

Age (years)	UL, µg/day
1-3	ND
4-8	ND
9-13	ND
14-18	ND
19 and older	ND
Pregnancy	ND
Lactation	ND

*ND: Not determinable, due to lack of data about adverse effects.

2.2.2 Scientific Committee for Food (SCF, 2003), EU

Acute and subchronic toxicity: SCF referred that no deaths had occurred after administering single doses of 25 000 mg phylloquinone per kg body weight orally or intraperitoneally to rats, mice and chicks. In addition, no adverse effects had occurred when administering daily oral doses of up to 2000 mg phylloquinone/kg body weight to rats for 30 days.

Carcinogenicity: SCF did not identify any experimental animal studies on carcinogenicity of vitamin K. The report from SCF also mentioned the small observational study by Golding et al, 1992 which had reported an association between neonatal intramuscular vitamin K injection and childhood cancer. This result, however, was refuted by later studies.

Genotoxicity: SCF considered that the limited available data did not allow an adequate evaluation of the genotoxic potential of phylloquinone at the gene or chromosome level.

Reproductive/developmental toxicity: No data on reproductive toxicity were available.

Human data: SCF cited two human studies in which no adverse effects were reported. In one uncontrolled experimental study, 10 mg/day phylloquinone was given to eight female elite long distance runners for 30 days (Craciun et al., 1998). In another 3x15-day crossover study including 36 healthy younger and older adults, the participants received a diet supplemented with broccoli (377 µg/day phylloquinone) or phylloquinone-fortified oil (417 µg/day phylloquinone) (Booth et al., 1999).

Risk characterisation: SCF stated the following:

“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.”

Derivation of UL: The SCF stated that there was no appropriate data from which to set a numerical upper limit for vitamin K.

Table 2.2.2-1 Tolerable upper intake levels (ULs) for vitamin K by the SCF (2003).

Age (years)	UL, µg/day
1-3	ND
4-6	ND
7-10	ND
11-14	ND
15-17	ND
Adults	ND

*ND: Not determinable.

2.2.3 Expert Group on Vitamins and Minerals (EVM, 2003), UK

The task of the Expert Groups on Vitamins and Minerals (EVM) was to consider the safety in long-term use of vitamin and mineral supplements sold under food law with a view to recommending maximum advisable levels of intake. Concerning vitamin K, the EVM concluded that there were insufficient data from studies in humans or animals to establish a safe upper level (SUL). The expert group considered that:

- Phylloquinone is not associated with adverse effects at high doses in animal studies.
- Acute doses up to 25 000 mg/kg bw did not cause fatalities in rats, mice or chicks.
- Human supplementation studies in small numbers of subjects suggest that, although having biological activity, doses of up to 10 mg/day for 1 month are not associated with adverse effects.

The EVM proposed a guidance level (GL) for safe upper intake of supplemental phylloquinone by applying an uncertainty factor of 10 for inter-individual variation (because of the very limited human database) to the dose of 10 mg/day supplemental phylloquinone that was consumed by eight female athletes (age 20-44) for 30 days with no reported adverse effects (Craciun et al., 1998). The resulting GL indicated that for guidance purposes, a daily supplemental intake of 1 mg/day would be unlikely to result in adverse effects. This is equivalent to 17 µg per kg body weight in a 60 kg adult. The GL applies to supplemental phylloquinone only. The UK expert group emphasised that GLs have been derived from limited data and are less secure than SULs. Furthermore, they stated that there are insufficient data available to provide guidance on total vitamin K intakes.

2.2.4 Rasmussen et al., 2006: A safe strategy for addition of vitamins and minerals to foods

Based on the GL by EVM, Rasmussen et al. (2006) later derived age-specific GLs for children and adolescents based on body weight^{0.75}. The age-specific GLs are listed in Table 2.2.4-1.

Table 2.2.4-1 Guidance levels (GL) for daily phylloquinone supplementation ($\mu\text{g}/\text{day}$) in age groups proposed by Rasmussen et al., 2006, based on the GL of the EVM (2003) adjusted for reference body weights.

Age (years)	GL, $\mu\text{g}/\text{day}$
1-3	270
4-6	370
7-10	500
11-14	670
15-17	870
Adults	1000

2.2.5 Nordic Nutrition Recommendations (NNR, 2012)

According to the NNR Project Group (2012), no evidence of toxicity associated with high intakes of any form of natural vitamin K has been reported. NNR (2012) referred to the SCF (2003) opinion, stating that there is no evidence of adverse effects associated with supplemental intakes of vitamin K in the form of phylloquinone of up to 10 mg/day for limited periods of time.

NNR also cited a publication reporting results from a double-blind randomised placebo-controlled trial (Cheung et al., 2008), in which 440 postmenopausal women with osteopenia had been randomised to receive 5 mg phylloquinone or placebo daily for two years. The trial had been extended to investigate long-term safety, with difference in Serious Adverse Events (SAE) as a predefined secondary outcome measure (<https://clinicaltrials.gov/show/NCT00150969>). The results of the trial supported that long-term daily intake of 5 mg phylloquinone did not cause adverse effects. The safety results were summarised as follows in the original publication:

“One or more adverse events were experienced by 384 women (87.3%) during the first 2 years of the study, but there were no significant differences between groups. Nausea and vomiting were reported in 11 women (5.1%) on vitamin K and ten women (4.5%) on placebo ($p=0.77$). From 2 to 4 years, 69.6% (188/270) had one or more adverse event: 72.2% (91/126) in the vitamin K group and 67.4% (97/144) on placebo ($p=0.46$). SAEs occurred in 9.1% (40/440) of participants: 6.9% (15/217) in the vitamin K group and 11.2% (25/223) in the placebo group. These included hospitalizations for pneumonia, heart failure, gastrointestinal bleeding, elective and non-elective surgeries, cancer, and death. Cancer incidence was lower in the vitamin K group than in the placebo group (three versus 12, $p=0.02$; HR=0.25, 95% CI 0.07 to 0.89). Higher mean serum vitamin K levels over the duration of the study correlated with lower cancer incidence ($p<0.05$). Because half of the cases were breast cancers (one in the vitamin K group and six in the placebo group), we calculated the Gail breast cancer risk score from baseline data and found that there was no difference between the vitamin K and the placebo groups (1.70% versus 1.71% risk of having invasive breast cancer in the next 5 years). There were five

deaths during the study and follow-up period: one woman on vitamin K (passenger in a car accident) and four women on placebo (three who died of cancers, and one who died in her sleep from arrhythmogenic right ventricular cardiomyopathy). There was no difference in health-related quality of life between groups.”

2.2.6 Summary of upper intake levels

Conclusions concerning ULs from previous reports on DRVs for vitamin K are shown in Table 2.2.6-1. No UL has been established due to lack of evidence.

The report from the UK Expert Group on Vitamins and Minerals (EVM, 2003) proposed a GL for safe upper intake of phylloquinone from supplements of 1 mg/day. This was based on an uncontrolled experimental study in eight female athletes who had received a daily dose of 10 mg phylloquinone per day for 30 days, with no reported adverse effects (Craciun et al., 1998).

NNR (2012) also cited a more recent double-blind randomised controlled trial with a larger sample size (n=440 randomised) providing a daily supplemental dose of 5 mg phylloquinone to postmenopausal women with osteopenia for a duration of up to four years (Cheung et al., 2008). There was no difference in adverse events between the groups. These findings support the GL proposed by EVM for phylloquinone of 1 mg/day, and provide evidence that the GL also applies to longer-term supplementation in older population subgroups than the study population of Craciun et al.

By adjusting for age-specific reference body weights, age-specific GLs for children and adolescents have been derived from the GL from EVM by Rasmussen et al. (2006). The resulting GLs range from 270 µg/day in 1-3-year-old children to 870 µg/day for 15-17-year-old adolescents.

No UL, SUL or GL exists that applies to dietary or supplemental intake of menaquinones or total vitamin K.

Table 2.2.6-1 Overview of existing tolerable upper intake levels (UL), safe upper levels (SUL) or guidance levels (GL) for vitamin K in adults set by various authorities.

	UL, SUL or GL	Based on	UF
IOM, 2002	ND		
SCF, 2003	ND		
EVM, 2003 ¹	1 mg/day	An uncontrolled experimental study giving 10 µg phylloquinone/day to eight female elite long distance runners (age 20-44; four amenorrhoeic for >1 year and four using oral contraceptives) for 30 days	10
NNR, 2012	ND		

ND: Not determined.

¹GL, applies to supplemental phylloquinone (vitamin K1) only.

3 Intakes of vitamin K

3.1 Dietary intake of vitamin K in Norway

Norwegian food composition data on vitamin K or data on habitual vitamin K intake in nationally representative samples of the population is not available.

In an osteoporosis substudy of a population-based health study carried out in Hordaland, Western Norway in 1997-2000, habitual dietary vitamin K intake was estimated in middle-aged (47-50) and older adults (71-75 years) by using a food frequency questionnaire (FFQ) (Apalset et al., 2010). While 76% of those invited participated in the substudy, the sample for data analysis after various exclusions constituted 49% of those invited (n=4461).

Food composition data for vitamin K1 were mostly based on databases developed by public authorities in Finland, Sweden and the USA, while data on vitamin K2 was obtained from the analyses by Schurgers and Vermeer (2000). For some typically Norwegian food products, HPLC-analyses were performed. Intake was estimated from diet only, as the most commonly used supplements in Norway did not contain vitamin K at the time of the study. Mean (SD) estimated dietary intakes of vitamin K in age and sex categories are shown in Table 3.1-1.

Table 3.1-1 Mean (SD) estimated habitual dietary intake (excluding supplements) of vitamin K1, vitamin K2, and total vitamin K ($\mu\text{g}/\text{day}$) in age and sex groups in the bone mineral density substudy of the Hordaland Health Study, 1997-2000 (n=4461) (Apalset et al., 2010).

	Women 47-50 years (n=1540)	Women 71-75 years (n=1035)	Men 47-50 years (n=993)	Men 71-75 years (n=893)
Vitamin K1	132 (116)	97 (91)	129 (119)	101 (79)
Vitamin K2	16 (7)	12 (6)	18 (8)	13 (6)
Vitamin K total	148 (117)	109 (93)	147 (120)	114 (80)

The 5- and 95-percentiles of dietary intakes of vitamin K were kindly provided by Ellen Margrete Apalset, University of Bergen/Haukeland University Hospital, and are shown in Table 3.1-2. The 95-percentiles of total vitamin K intakes ranged from 261 to 329 $\mu\text{g}/\text{day}$. They were higher in middle-aged (47-50 years) than in older people (71-75 years), and, within both age cohorts, they were higher in women than in men (Table 3.1-2).

Table 3.1-2 P5 and P95 of estimated habitual dietary intake (excluding supplements) of vitamin K1, vitamin K2, and total vitamin K ($\mu\text{g}/\text{day}$) in in age and sex groups in the bone mineral density substudy of the Hordaland Health Study, 1997-2000 (n=5773)¹.

	Women 47-50 years (n=1690)	Women 71-75 years (n=1569)	Men 47-50 years (n=1276)	Men 71-75 years (n=1238)
P5				
Vitamin K1	38	20	45	30
Vitamin K2	7	4	8	5
Vitamin K total	49	26	58	39
P95				
Vitamin K1	315	265	288	247
Vitamin K2	29	22	33	25
Vitamin K total	329	279	314	261

¹Note: 2.5% highest and 2.5% lowest energy intakes (n=300) and 81 persons using warfarin are excluded. Results provided courtesy of Ellen Margrete Apalset, personal communication.

Data about habitual dietary intake of vitamin K in younger adults, adolescents and children in Norway is not available.

3.2 Dietary intake of vitamin K in other countries

3.2.1 Europe

In their 2017 opinion on DRV for vitamin K (EFSA, 2017), EFSA summarised vitamin K intakes calculated from dietary surveys in various European countries. The EFSA Panel noted that there are large uncertainties in the food composition data and available consumption data related to phylloquinone, individual menaquinones and total vitamin K. Estimated average intakes of 'total vitamin K' for nine EU countries ranged between:

- 36 and 53 $\mu\text{g}/\text{day}$ in children aged 1 to <3 years
- 42 and 93 $\mu\text{g}/\text{day}$ in children aged 3 to <10 years
- 68 and 143 $\mu\text{g}/\text{day}$ in children aged 10 to <18 years
- 72 and 196 $\mu\text{g}/\text{day}$ in adults (≥ 18 years)

Phylloquinone was the major consumed form of vitamin K. The main food group contributing to total vitamin K intakes was 'vegetables and vegetable products'. Leafy vegetables followed by Brassica vegetables were the most important contributors for all age groups 1 year and older. In addition, composite dishes were contributors to total vitamin K intakes, probably at least partly due to vegetable-based ingredients in the dishes, as well as (to a lower extent) the food groups 'animal and vegetable fats and oils', and 'legumes, nuts, oilseeds and spices'.

3.2.2 Sweden

The most recent data on vitamin K from Sweden from RIKSMATEN 2010-11 in adults 18-80 years (Amcoff et al., 2012) were reported by EFSA (2017) and are listed in Table 3.2.2-1. The latest dietary survey in children and adolescents was performed in 2003, and vitamin K intakes were not calculated (Barbieri et al., 2006).

Table 3.2.2-1 Dietary intakes of vitamin K ($\mu\text{g/day}$) in adults and older people in Sweden, reported in EFSA (2017).

Age group	Study	N	Mean	Median	P5	P95
≥ 75 years	Riksmaten 2010-11 ¹	42	104	87	NC	NC
65-<75 years	Riksmaten 2010-11 ¹	127	92	80	37	167
18-<65 years	Riksmaten 2010-11 ¹	623	91	77	31	184

NC: Not calculated due to fewer than 60 subjects.

¹Amcoff E, Edberg A, Barbieri HE, Lindroos AK, Nälsén C, Pearson M, Lemming EW. Riksmaten – vuxna 2010–11. Livsmedels- och näringsintag bland vuxna i Sverige. Resultat från matvaneundersökning utförd 2010–11. Livsmedelsverket, Uppsala, 2012. ISBN 978-91-7714-216-4. Available at: <https://www.livsmedelsverket.se/matvanor-halsa--miljo/kostrad-och-matvanor/matvanor---undersokningar/riksmaten-2010-11---vuxna>

3.2.3 Finland

In Finland, dietary surveys have been performed relatively recently in both children, adolescents and adults. Calculated intakes of vitamin K reported by EFSA (2017) are listed in Table 3.2.3-1.

Table 3.2.3-1 Dietary intakes of vitamin K ($\mu\text{g/day}$) in Finland, reported in EFSA (2017).

Age group	Study	N	Mean	Median	P5	P95
65-<75 years	FINDIET 2012 ¹	210	94	81	32	200
18-<65 years	FINDIET 2012 ¹	585	92	81	30	180
10-<18 years	NWSSP ²	136	73	70	29	129
3-<10 years	DIPP ³	381	45	40	21	81
1-<3 years	DIPP ³	245	42	39	15	74

¹Helldán A, Raulio S, Kosola M, Tapanainen H, Ovaskainen ML, Virtanen S. Finravinto 2012-tutkimus. The National FINDIET 2012 Survey. THL Report 16/2013. Available at: <https://www.julkari.fi/handle/10024/110839>

²Nutrition and Wellbeing of Secondary School Pupils (NWSSP), age 13-15 years. Hoppu U, Lehtisalo J, Tapanainen H, Pietinen P. Dietary habits and nutrient intake of Finnish adolescents. *Public Health Nutr* 2010;13(6A):965–972.

³The Type 1 Diabetes Prediction and Prevention (DIPP) birth cohort study. Kyttälä P1, Erkkola M, Kronberg-Kippilä C, Tapanainen H, Veijola R, Simell O, Knip M, Virtanen SM. Food consumption and nutrient intake in Finnish 1-6-year-old children. *Public Health Nutr* 2010;13(6A):947-56.

3.2.4 Denmark

Through communication with the Danish Veterinary and Food Administration, NFSA has obtained data on dietary vitamin K intake in Denmark calculated by the Technical University of Denmark (DTU).

A nationally representative survey of diet and physical activity in the Danish population aged 4-75 years was carried out in 2011-2013 (DANSDA) (DTU, 2015). Diet was assessed through a 4-day food record. Vitamin K was not part of the standard battery of vitamins calculated, but it has been possible to perform the calculations in the programme used for DANSDA 2011-13, using the Danish food composition database (<http://frida.fooddata.dk/>) and supplementing missing values with data from the USDA food composition database (<https://ndb.nal.usda.gov/ndb/>). The intake estimates were considered to be of 'medium' uncertainty measured on EFSA's scale, defined as follows: "Some or only incomplete data available; evidence provided in small number of references; authors' or experts' conclusions vary, or limited evidence from field observations, or solid and complete data available from other species which can be extrapolated to the species being considered."

Vitamin K intake for 1-3-year-old children could not be estimated because of missing food composition data for vitamin K for a number of foods commonly consumed by toddlers. The vitamin K intakes estimated for Danes aged 4 to 75 years are listed in Table 3.2.4-1.

Table 3.2.4-1 Estimated mean, median and 95-percentile of dietary intake of vitamin K ($\mu\text{g/day}$) in age and sex groups in DANSDA 2011-2013.

Sex	Age range	N	Mean	Median	P95
Male	4 – 6	108	49	45	87
	7 – 10	143	57	48	122
	11 – 14	135	61	57	116
	15 – 17	81	68	70	123
	18 – 75	1464	103	91	210
Female	4 – 6	95	48	44	85
	7 – 10	153	56	49	108
	11 – 14	124	59	52	124
	15 – 17	91	63	54	131
	18 – 75	1552	97	86	199
Both	4 – 6	203	48	45	87
	7 – 10	296	56	49	116
	11 - 14	259	60	54	120
	15 - 17	172	65	60	124
	18 - 75	3016	100	89	206

3.3 Summary of dietary intake of vitamin K in Norway and the other Nordic countries

To our knowledge, information about dietary intake of vitamin K in Norway is available only in a sample of middle-aged (47-50 years) and older adults (71-75 years) participating in a substudy of a population based health study in Western Norway carried out in 1997-2000. Mean estimated intakes of total vitamin K were 147 and 148 µg/day in middle-aged men and women, respectively, while they were 114 and 109 µg/day in older men and women, respectively. The 95-percentiles of total vitamin K intake ranged from 261 in older men to 329 µg/day in middle-aged women.

Intake distributions in all age groups in the population above 1 year (mean intakes, median, P5, P95) are not available in data from Norway, but have recently been published for several European countries by EFSA. Mean total vitamin K intakes in the Norwegian data were, at least in the middle-aged group (47-50 years), higher than mean intakes estimated for adults in dietary surveys carried out in Denmark, Sweden and Finland. It is difficult to appraise the degree to which the differences may be due to methodological differences (see section 5.1). Based on knowledge about the various Nordic diets, it may be assumed that Nordic diets typically do not differ substantially with regard to vitamin K consumption. Data from nationally representative dietary surveys in Sweden, Finland and Denmark indicate that average intakes of total vitamin K in the Nordic countries are in the magnitude of 100 µg/day in adults, while 95-percentiles suggest that the highest intakes levels are in the magnitude of 200 µg/day (adults).

Since the GL for phylloquinone applies to supplemental phylloquinone only, VKM has not calculated intake scenarios as requested in the terms of reference.

4 Assessment of the suggested maximum limits

The present assessment is performed for phyloquinone (vitamin K1) only, as there is no available UL, SUL or GL for menaquinones (vitamin K2) due to lack of data.

The Expert Group on Vitamins and Minerals (EVM, 2003) proposed that for guidance purposes, a daily supplemental intake of 1 mg/day in adults would be unlikely to result in adverse effects. The safety of an intake at this guidance level is supported by a later double-blinded randomised controlled trial performed in postmenopausal women, cited by the fifth Nordic Nutrition Recommendations 2012 (Cheung et al., 2008). Age-specific GLs for children and adolescents were derived by adjusting for body weight^{0.75} by Rasmussen et al. (2006), ranging from 270 µg/day in 1-3-year-olds to 870 µg/day in 15-17-year-olds.

Consequently, scenarios for alternative maximum limits for vitamin K in supplements indicate that a maximum limit of:

- 100 µg/day or 200 µg/day is below GL in all age groups
- 300 µg/day exceeds GL for 1-3 year-old children and is below GL in all other age groups
- 600 µg/day exceeds GL for all age groups up to and including 10 years and is below GL in all age groups 11 years and older
- 800 µg/day exceeds GL for all age groups up to and including 14 years and is below GL in all age groups 15 years and older.

It should be noted that persons using anticoagulant drugs with vitamin K antagonist action (warfarin) should be monitored by their physician and should avoid making major sudden changes in their vitamin K intake.

5 Uncertainties

5.1 Uncertainties related to quantifying dietary vitamin K intake

As discussed by EFSA (2017), there are large uncertainties in the food composition data for vitamin K and consequently in the calculation of total vitamin K intake from the diet. The proportion of food composition values borrowed from other countries vary widely between countries. EFSA (2017) also stressed the uncertainty arising from the notion that for some countries, intake data on 'total vitamin K' provided to the EFSA database seemed to represent phylloquinone only, whereas for other countries (e.g. Sweden), it corresponded to the sum of phylloquinone and menaquinones. Due to the lack of data on vitamin K intakes in all age groups in the population in Norway, VKM has considered data from other Nordic countries. Based on the published results from the Nordic countries, however, VKM has not been able to appraise the degree to which between-country differences in estimated intakes are due to actual differences in the consumption of foods providing vitamin K, and to what degree the differences arise from methodologic limitations related to varying food composition data and calculation methods used. Means and 95-percentiles of calculated total vitamin K intakes in middle-aged and older Norwegians in the population-based Hordaland Health Study (Apalset et al., 2010; Apalset 2018, personal communication) were higher than the intakes estimated for adults from dietary surveys in other Nordic countries, but this may not necessarily imply a true higher consumption of vitamin K in Norway. Rather, it could be the result of the thorough effort to obtain and incorporate complete food composition data for phylloquinone and menaquinones in the Norwegian cohort study where this nutrient was of particular focus.

5.2 Uncertainties related to evaluating maximum limits for vitamin K in food supplements

Concerning assessment of maximum limits in food supplements, there is large uncertainty related to the upper level that could be considered safe. No UL for vitamin K has been established by the IOM, the SCF/EFSA or the NNR, since there is no data on toxicity or adverse effects of vitamin K to inform a dose-response assessment, no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL). To evaluate the potential maximum limits suggested by the NFSA in the terms of reference for the current opinion, VKM has based its conclusions on the guidance level (GL) proposed by the EVM in 2003 which applies to supplemental intake of phylloquinone only. The basis for this GL was an uncontrolled 30-day supplementation study giving 10 mg phylloquinone per day to eight female athletes, and dividing by a UF of 10. The EVM emphasised that this figure was provided for guidance purposes and that no true Safe Upper Level (SUL) could be established due to insufficient data in humans or animals. This GL was supported by a double-blind randomised study cited in the NNR from 2012, in which 440 postmenopausal women with osteopenia received a daily supplement of 5 mg phylloquinone or placebo for up

to four years without any difference in adverse events between the randomised groups. GL for children and adolescents are not based on data, but have merely been extrapolated from the GL for adults based on body weight. VKM emphasises that no literature search for studies on vitamin K has been conducted for the current opinion, as this was outside the scope of the terms of reference from NFSA. There may indeed be relevant literature published after 2003 which has not been taken into account for the present assessment.

6 Answers to the terms of reference

The Norwegian Food Safety Authority (NFSA, Mattilsynet) has requested the Norwegian Scientific Committee for Food and Environment (VKM) to assess the intake of vitamin K from the diet, including fortified products, in all age groups in the population above 1 year.

As there is no data on vitamin K in the Norwegian food composition data base (KBS), VKM is requested to evaluate if other relevant intake data can be used - included Danish intake data estimated by the National Food Institute in Denmark (DTU) and the EFSA Scientific Opinion on Dietary reference values for vitamin K (2017).

VKM is also requested to conduct scenario estimations to illustrate the consequences of establishing maximum limits for vitamin K at 100, 200, 300, 600 or 800 µg/day in food supplements. VKM has been requested to base its opinion on conclusions from previous risk assessments of vitamin K.

To the best of our knowledge, information about dietary intake of vitamin K in Norway is available only in a sample of middle-aged (47-50 years) and older adults (71-75 years) participating in a substudy of a population-based health study in Western Norway carried out in 1997-2000. Mean estimated intakes of total vitamin K were 147 and 148 µg/day in middle-aged men and women, respectively, while they were 114 and 109 µg/day in older men and women, respectively. The corresponding 95-percentiles were 314 and 329 µg/day in middle aged men and women; 261 and 279 µg/day in older men and women.

To illustrate the consequences of establishing maximum limits for vitamin K at 100, 200, 300, 600 or 800 µg/day in food supplements, VKM has compared these suggested alternative limits to age-specific guidance levels (GL) for supplementary phyloquinone. The GLs are: 1000 µg/day for adults, 870 µg/day for age 15-17 years, 670 µg/day for age 11-14 years, 500 µg/day for age 7-10 years, 370 µg/day for age 4-6 years and 270 µg/day for age 1-3 years (EVM, 2003; Rasmussen et al., 2006).

VKM concludes that:

- In adults and adolescents 15-17 years old, maximum limits of 100, 200, 300, 600 and 800 µg/day are below GL.
- In adolescents 11-14 years old, maximum limits of 100, 200, 300 and 600 µg/day are below GL while the maximum limit of 800 µg exceeds GL.
- In children 4-10 years old, maximum limits of 100, 200 and 300 µg/day are below GL while maximum limits of 600 µg/day and 800 µg/day exceeds GL.
- In children 1-3 years old, maximum limits of 100 µg/day and 200 µg/day are below GL while maximum limits of 300, 600 and 800 µg/day exceeds GL.

VKM notes that the current conclusions apply to phylloquinone (vitamin K1) only, while there is insufficient evidence to appraise potential health consequences of maximum limits of menaquinones (vitamin K2).

It was not within the scope of the current opinion to re-evaluate tolerable upper intake levels or safe upper levels of vitamin K intake, and a literature search has not been performed for the current opinion.

7 Data gaps

The distribution of intakes of phylloquinone and menaquinones across all age groups in the population of Norway is not known. There is a need to obtain and incorporate data on phylloquinone and menaquinones in the Norwegian food composition database and to enable calculation of vitamin K intake in dietary surveys.

According to previous reports that have reviewed the evidence, there is a lack of data from human and animal studies that can be used to establish tolerable upper intake levels or safe upper levels for phylloquinone and menaquinones. However, years have passed since the publication of the previous risk assessments, and vitamin K has been the subject of considerable attention in health research during the 2000s. For the current opinion, VKM has not performed a systematic literature review and thus cannot exclude the possibility that relevant human and animal data on the safety of vitamin K supplementation may be available. VKM recommends that an updated risk assessment of vitamin K is carried out with the purpose of establishing UL for vitamin K if possible.

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