Vitamin K2 - Menaquinone-7

bw	body weight
CNS	Chinese Nutrition Society
CRN	Council for Responsible Nutrition
DRI	dietary reference intake
EC SCF	European Commission Scientific Committee on Food
EFSA	European Food Safety Authority
EVM	Expert Group on Vitamins and Minerals
HOI	highest observed intake level
ICMR-NIN	Indian Council of Medical Research - National Institute of Nutrition
IOM	Institute of Medicine
IU	international unit
JECFA	Joint FAO/WHO Expert Committee on Food Additives
KNS	Korean Nutrition Society
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
NDA	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NIH	National Institute of Health
NOAEL	no observed adverse effect level
NOEL	no observed effect level
RCT	randomized clinical trial
SUL	safe upper level
UF	uncertainty factor
UL	tolerable upper intake level

Introduction

Vitamin K is a group of fat-soluble vitamins that are essential for biosynthesis of proteins involved in blood coagulation and metabolic pathways in bone and other tissues. This group includes two natural vitamers: vitamins K_1 (phylloquinone) and K_2 (menaquinone) (IOM 2001; Marles et al. 2017; Drake 2022; Zhang et al. 2024). Menaquinones constitute a group of vitamin K2 compounds characterized by structurally variable isoprenoid side chains, commonly designated as MK-n, where "n" indicates the number of isoprene units, ranging from 4 to 13. The

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predominant dietary forms include MK-4, mostly found in animal-derived foods, and MK-7 – MK-10, primarily present in fermented foods or dairy products (Sato et al. 2020; Drake 2022). MK-4 is distinctive in its ability to be synthesized endogenously in animal tissues via a conversion pathway from phylloquinone (vitamin K1), MK-4, MK-7, and MK-9 (Ellis et al. 2022). Conversely, long-chain menaquinones (e.g., MK-7) are predominantly produced by bacterial biosynthesis and are ingested through fermented foods or generated endogenously by gut microbiota, although the efficiency of colonic absorption remains uncertain (Beulens et al. 2013; Marles et al. 2017).

Bioavailability

Intestinal absorption of menaquinones occurs predominantly in the duodenum and jejunum, where they are subsequently incorporated into chylomicrons, which facilitate transport via the lymphatic system into systemic circulation (Marles et al. 2017; Zhang et al. 2024). Menaquinones with longer side chains (e.g., MK-7) exhibit increased plasma half-lives and enhanced distribution to extrahepatic tissues relative to both phylloquinones and shorter-chain menaquinones, such as MK-4 (Sato et al. 2012; Halder et al. 2019). For example, the half-life of MK-7 is estimated to be approximately 72 hours, while that of MK-4 is approximately one hour (Schurgers et al. 2007; Zhang et al. 2024). In addition, the extended isoprenoid side chains in menaquinones augment their lipophilicity, thereby contributing to their prolonged biodistribution within the body (Beulens et al. 2013). As such, MK-7 sustains elevated circulating serum concentrations over extended durations relative to MK-4 (Halder et al. 2019; Zhang et al. 2014).

MK-7 has been shown to have higher efficacy at lower doses in clinical trials because of such differences in bioavailability (Sato et al. 2020). Human clinical trials identified in the literature search were conducted with doses ranging from 58-999 µg MK-7 per day, as discussed below. For comparison, available clinical studies conducted with MK-4 have employed doses ranging from 1,500 µg per day to 135 mg per day (45 mg or 45,000 ug, three times daily) (Asakura et al. 2001; Ushiroyama et al. 2002; Nakamura et al. 2014; Koitaya et al. 2014).

Differences in bioavailability between MK-4 and MK-7, as well as variations dosage and study design, may influence the relevance of safety conclusions drawn for MK-7. Therefore, the present

chapter is focused on the available clinical outcomes related to safety of MK-7 and the development of a supplemental UL or HOI[1] level for MK-7 in adults.[2]

Safety Considerations

Vitamin K acts as a coenzyme for the vitamin K-dependent carboxylase enzyme, which is essential for the activation of proteins that play key roles in blood clotting, bone metabolism, and other physiological processes (NIH 2021; Drake 2022). Prothrombin (i.e., clotting factor II), a vitamin K-dependent protein in plasma, is directly involved in the coagulation process. Both vitamin K1 and vitamin K2 (including MK-7) have been shown to attenuate the pharmacological effect of anticoagulants in clinical studies, with varying thresholds (Schurgers et al. 2004, 2007; Theuwissen et al. 2013). Vitamin K antagonists (VKAs), such as warfarin, phenprocoumon, acenocoumarol, and tioclomarol, inhibit coagulation through antagonizing the procoagulant action of vitamin K, thereby disturbing the coagulation cascade. As a result, co-administration of vitamin K (including MK-7) with VKAs is contraindicated (NIH 2021; Drake 2022). Conversely, the EFSA (2008) reviewed unpublished studies that demonstrated MK-7 did not affect endogenous thrombin potential or thrombin peak height in healthy adults not taking anticoagulants, indicating that no activation of the clotting system was observed (Vermeer et al. 2007a,b).

Available animal toxicological studies on MK-7 have not shown effects on coagulation parameters (Pucaj et al. 2011; Hwang et al. 2024). In subchronic oral toxicity studies in rats, the authors did not consider observed changes in blood coagulation parameters, such as prothrombin time (PT) or activated partial thromboplastin time (APTT), to be of toxicological significance. The study authors noted that this was due to the lack of dose relationship (Pucaj et al. 2011) and the lack of effects in the main study group (Hwang et al. 2024).

MK-7 has been extensively studied for its safety and efficacy in controlled clinical trials involving hundreds of participants from diverse populations. No serious adverse effects associated with supplementation were reported across the 45 studies identified that met the inclusion criteria for

[1] HOI is defined as the highest intake level with adequate data to establish that adverse effects do not occur at intakes up to that level.
[2] Limited human intervention trials with MK-4 were identified; data specific to this menaquinone are included in the discussion for context relative to that of MK-7 only.

this review, which tested doses ranging from 58.3-462.8 µg per day for up to two years. Most studies reported specifically on incidence of adverse events or side effects; only a few studies did not include monitoring for such in the methodology. Seven of the studies identified were designed to specifically include clinical chemistry parameters relevant to potential effects on coagulation following administration of MK-7, as summarized below. No adverse effects on any of the parameters assessed were reported.

- In a double-blinded, placebo-controlled, randomized intervention trial ("RenaKvit" trial), hemodialysis patients were dosed with 360 µg per day or placebo for up to two years (Bladbjerg et al. 2023; Levy-Schousboe et al. 2021, 2023). In one analysis of this cohort, intervention for 52 weeks resulted in no significant effects on biomarkers of coagulation activation (thrombin generation and prothrombin fragment concentrations), clot activities of vitamin K-dependent coagulation factors (II (FII:C), VII (FVII:C), IX (FIX:C), and X (FX:C), or vascular events compared to the placebo group (Bladbjerg et al. 2023). Other publications with this same cohort reported the number of thromboembolic events was higher in the placebo group compared to the treated group (360 µg MK-7 per day for two years; p value of 0.02) due to "more events in one placebo-supplemented participant" (Levy-Schousboe et al. 2021, 2023).
- PT time was determined to be the same between placebo and MK-7 (360 µg per day) groups of vitamin k-deficient kidney transplant recipients after 12 weeks (Eelderink et al. 2023).
- No effects on thrombin generation were observed in a randomized, double-blind, controlled trial in healthy adults following intervention with 0, 10, 20, 45, 90, 180 or 360 µg per day for three months (Theuwissen et al. 2012).
- In a prospective, randomized, crossover intervention trial, hemodialysis patients were given 360 µg per day for six weeks. After a three-week washout period, the same patients were given a vitamin K-rich diet. No statistically significant differences were found in international normalized ratios (INRs) between groups (Lentz et al. 2022).
- Inaba et al. (2015) published two double-blind, randomized, controlled trials. In the first, post-menopausal women were administered 0, 50, 100, or 200 µg per day for four weeks. In the second study, healthy adults were dosed with 100 µg per day for 12 weeks. While PT-

INR was not assessed in the first study, there were no statistically significant effects on this parameter in the second study.

- In an observational case-series, no effects on "bleeding time and clotting time" were observed following intervention with 100 µg per day in adults with muscle cramps for three months; however, no data on these parameters were presented in the publication (Mehta et al. 2010).
- Ren et al. (2021) administered 90 µg per day to healthy adults, finding no statistically significant differences in PT, APTT, thrombin time, or activities of coagulation factors II, VII, IX, and X after 30 days. Information on study design was limited.

Four additional studies stated that adverse events potentially related to coagulation (described as thrombotic, clotting, and/or vascular) did not occur following intervention with MK-7 or that incidences were not statistically significantly different between groups (Witham et al., 2020; Rahimi Sakek et al. 2021; Haroon et al. 2023; Naiyarakseree et al. 2023). For example, in a one-year randomized, double-blind, placebo-controlled study, the incidence of "vascular" events was similar in patients with chronic kidney disease receiving MK-7 (400 µg per day) or placebo (Witham et al. 2020). Similarly, Naiyarakseree et al. (2023) administered 375 µg per day for six months and reported that the incidence of arteriovenous fistula thrombosis to be the same between the placebo and intervention groups. While these incidences of potentially related adverse events were reported, coagulation-related clinical chemistry parameters were not assessed in these studies.

The lack of serious adverse effects in interventional studies with MK-7 is corroborated by other long-term, high-dose trials that included concomitant exposures. One randomized, double-blind, multicenter trial in men with aortic valve calcification administered 720 µg plus 25 µg vitamin D per day or placebo for two years; no differences in PT-INR or adverse events occurred between groups (Diederichsen et al. 2022). In another randomized controlled trial, hemodialysis patients with atrial fibrillation received VKAs or 10 mg per day rivaroxaban with or without 2,000 µg thrice weekly for 1.5 years (De Vriese et al. 2020). The incidence of cardiovascular events was similar between groups, and bleeding outcomes were significantly higher in the VKA group. Overall, data from multiple clinical trials indicate that MK-7 is well tolerated and not associated with significant adverse events in humans.

Official Reviews

UL values specifically for MK-7 have not been derived by the authoritative agencies listed below. Information on assessments for vitamin K1 and/or vitamin K2 are included for completeness.

IOM (2001). The IOM found no reports of adverse effects for vitamin K_1 or vitamin K2; hence, it concluded that a quantitative risk assessment could not be conducted, and no UL value was established.

Expert Group on Vitamins and Minerals (EVM 2003). In its review of vitamin K, the UK's EVM noted that "there are clear differences in the toxicity of different forms of vitamin K" and that "few data are available relating to" vitamin K2. No human clinical or toxicological studies conducted with vitamin K2 were included in the review. The EVM derived a guidance level for supplemental vitamin K1 only.

European Food Safety Authority (EFSA 2006). The EFSA (2006)[3] determined that there were no "appropriate data from which to set a numerical upper limit for vitamin K" (all forms).

In a separate assessment, the EFSA (2008) delivered its Scientific Opinion on the safety of a vitamin K2-rich extract for specified proposed uses and use levels as a novel food. The vitamin K2 extract consisted primarily of MK-7, and to a lesser extent MK-6. The EFSA (2008) summarized the available human clinical and animal toxicology studies on vitamin K2. The Panel noted that available studies on MK-7 and MK-6 were limited and, therefore, read-across from studies with MK-4 was employed based on "the similar metabolic fate of the vitamin K derivatives, and the structural similarity of the vitamin K2 homologues." The key study identified by the EFSA was a one-year dietary toxicity study in rats administered concentrations of a synthetic MK-4 equivalent to 0, 20, 100, or 500 mg per kg bw per day (Hosokawa et al. 1995). The EFSA (2008) identified the lowest dose of 20 mg MK-4 per kg bw per day as the LOAEL, citing "that a significant decrease in prothrombin time (PT) in all treated males, pointing at decreased

[3] Originally published by the EC SCF in 2003 as SCF/CS/NUT/UPPLEV/32 Final.

time to form blood clots, could be an adverse effect." The EFSA also referred to unpublished human interventional studies demonstrating a lack of effects on blood clotting parameters in children and adults up to 45 and 360 µg MK-7 per day, respectively (Van Summeren et al. 2007; Vermeer et al. 2007a,b). Based on the preclinical toxicology study with MK-4, the human interventional studies with MK-7, and dietary intake estimates of MK-7 in the oil, the EFSA concluded use of the oil (meeting the provided specifications) was "not of safety concern."

Chinese Nutrition Society (CNS 2023). The CNS stated that "the UL value still could not be established" for vitamin K, including vitamin K2. However, an adequate intake (AI) level of 80 µg total vitamin K per day was derived for adults.

Indian Council of Medical Research - National Institute of Nutrition (ICMR-NIN 2020). The ICMR-NIN did not include vitamin K forms, including vitamin K2, when deriving UL values.

Korean Nutrition Society (KNS 2020). The KNS published its general approach to evaluating data for setting DRI values. The KNS did not publish a UL for vitamin K (total), and it does not appear that vitamin K2 was assessed.

CRN Recommendations

The previous (3rd) edition of CRN's *Vitamin and Mineral Safety* derived a single UL value for vitamin K (vitamin K1 and vitamin K2) of 10 mg per day based on a single human clinical study with vitamin K1 (Craciun et al. 1998). The goal of the present chapter was to derive an UL or HOI value specific to supplemental MK-7 (one vitamin K2 menaquinone) in adults following CRN's updated methodology. While not all human clinical trials are specifically designed to evaluate adverse effects, no new trials were identified that reported any serious adverse effects with supplemental MK-7. As with any assessment in which not all available data are reviewed, inherent uncertainties with the risk assessment and selection of the UL or HOI are recognized.

CRN's safety methodology for deriving supplemental UL or HOI values prioritizes data from human studies, when available. Approximately 41 human clinical trials in 43 publications since the 3rd edition (2014) were identified and subsequently reviewed that met the inclusion criteria for

the current chapter. Two earlier studies were also identified via secondary sources. Given the lack of any serious adverse effects observed across clinical studies with MK-7, a supplemental HOI level is derived for vitamin K7. The table below summarizes the key human clinical studies considered in deriving the supplemental HOI level by CRN according to its principal points of departure for risk assessment (as described in the Methods chapter).[4]

Key Studies Considered for the CRN HOI for Menaquinone-7 (MK-7) in Adults

Reference	Study Design	Participant Description	No. of Subjects	Dose(s) (ug/day)	Duration	Parameters Assessed	NOAEL (ug/day)
Witham et al. (2020)	Randomized, double-blind, placebo-controlled	Patients with chronic kidney diseases	159	0, 400	1 year	Incidence of vascular events	400
Naiyarakseree et al. (2023)	Multicenter, randomized, placebo-controlled	Patients on chronic dialysis	96	0, 375	6 months	Incidence of thrombosis	375
Bladbjerg et al. (2023)	Multicenter, randomized, double-blind, placebo-controlled	Patients on chronic dialysis	123	0, 360	1 year	Thrombin generation; prothrombin fragment concentration; clotting activity of K-depending coagulation factors	360
Theuwissen et al. (2012)	Randomized, double-blind, placebo-controlled	Healthy adults	42	0, 10, 20, 45, 90, 180, 360	3 months	Thrombin generation	360
Eelderink et al. (2023)	Randomized, double-blind, placebo-controlled	Patients with vitamin K-deficiency and kidney transplant	40	0, 360	3 months	Prothrombin time	360
Rahimi Sakak et al. (2021)	Randomized, double-blind, placebo-controlled	Patients with type 2 diabetes	68	0, 360	3 months	Incidence of blood clotting reactions	360

As discussed in the *Safety Considerations* section, the potential effects of vitamin K vitamers on

[4] Where numerous relevant studies were identified, those most pertinent to the HOI derivation are included in the table as representative studies. Prioritization was given to studies at dose levels informing the HOI and studies with higher weighting based on CRN's Methods (e.g., duration, number of participants, randomization, etc.).

the coagulation process have been well established in patients taking VKA anticoagulants. No changes in clinical chemistry parameters relevant to potential effects on coagulation were observed in interventional studies in individuals not taking VKA medications following administration of MK-7. Administration of MK-7 in clinical studies was not associated with an increase in coagulation-related adverse events at doses ranging from 154-400 µg per day for up to two years (Witham et al., 2020; Rahimi Sakek et al. 2021; Haroon et al. 2023; Naiyarakseree et al. 2023). In addition, no effects on coagulation-related clinical chemistry parameters were observed in studies with doses ranging from 10-360 µg MK-7 per day for up to one year (Mehta et al. 2010; Theuwissen et al. 2012; Inaba et al. 2015; Ren et al. 2021; Lentz et al. 2022; Bladbjerg et al. 2023; Eelderink et al. 2023). The RenaKvit trial provides the most comprehensive assessment of relevant clinical chemistry parameters, which were analyzed following administration of 360 µg per day in chronic dialysis patients for one year (Bladbjerg et al. 2023). In addition, incidence of thrombosis was similar between the placebo group and patients administered 375 µg MK-7 per day for six months in the study published by Naiyarakseree et al. (2023). One other study conducted at 400 µg per day was identified that reported differences in incidence of "vascular" events; however, this publication did not provide detailed descriptions that would allow analysis of coagulation-related events specifically (Witham et al. 2020; Naiyarakseree et al. 2023).

No serious adverse effects were reported in any human intervention study with MK-7 meeting the inclusion criteria for this review; studies administered doses ranging from 58.3-462.8 µg per day for four weeks to two years. Based on the available data, 375 µg per day from the Naiyarakseree et al. (2023) study is identified as the NOAEL for MK-7 for healthy adults following the CRN process. As described in CRN's Methods, if the supplemental intake dose-response relationship is identified from the strongest data and assessed conservatively, no additional uncertainty factor is needed (that is, the implicit UF is 1.0). Consistent with CRN's methodology, an UF of 1 is applied to yield an HOI level of 375 µg per day for adults for supplemental MK-7.

Because of the strong antagonistic interaction of vitamin K vitamers (i.e., vitamin K1 and vitamin K2) with VKA anticoagulant drugs (e.g., warfarin, phenprocoumon, acenocoumarol, and tioclomarol) and impact on INR, the HOI level for MK-7 does not apply to individuals taking such medications. Individuals taking such medication, or otherwise with known bleeding

disorders, should consult with their physician regarding use of vitamin K-containing supplements, including MK-7.

Quantitative Summary for Menaquinone-7 (MK-7)

CRN HOI level (2025), supplemental intake	375 µg/day[a]
IOM UL (2001)	Not determined
EFSA UL (2006)	Not determined[b]
EVM (2003)	Not determined[c]
CNS (2023)	Not determined
ICMR-NIN (2020)	Not evaluated
KNS (2020)	Not evaluated

[a] Does not apply to individuals taking VKA anticoagulant medications or otherwise with known bleeding disorders.
[b] The EFSA (2008) determined that estimated 97.5 percentile intakes up to 115 µg MK-7 per day were "not of safety concern."
[c] The EVM (2003) derived a guidance level for supplemental vitamin K1 only.

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