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High single doses of vitamin D via food supplements at intervals of days or weeks associated with health risks

The effects of combination preparations containing high doses of vitamins D and K2 have yet to be truly studied

In brief

- Food supplements containing vitamin D are available in various dosages. Preparations are also available in which very high single doses ("bolus doses") of vitamin D are to be taken at intervals of several days to weeks. Some preparations also contain vitamin K2.

- High bolus doses of vitamin D (e.g. 500 micrograms (µg) every 20 days) can lead to vitamin D concentrations in the blood that, according to studies, pose health risks, especially for people who already have a very good supply of vitamin D.

- Studies have shown that taking very high bolus doses of vitamin D can increase the risk of, for example, falls and bone fractures. Other studies have found neither health impairments (at lower doses in some cases) nor health benefits.

- According to the German Federal Institute for Risk Assessment (BfR), food supplements that are to be taken as bolus doses at specific intervals also pose a problem in that they increase the risk of improper intake. This means that they may be taken more frequently than intended, e.g. daily instead of every 20, 10 or

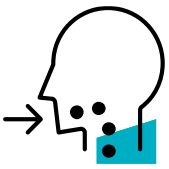
7 days. This increases the risk of health impairments.

- For cases in which supplementation is necessary, the BfR recommends taking a lower-dose preparation daily. The BfR recommends a maximum amount of 20 µg of vitamin D per daily dose in food supplements, as this is not expected to pose any health risks in the long term, even when other sources of vitamin D are taken into account. Bolus doses of vitamin D and vitamin K should only be taken on medical advice and under medical supervision.

- This opinion assesses the intake of high bolus doses of vitamin D via food supplements. It does not apply to medical drugs containing vitamin D in different doses and with different application regimens, which may be prescribed by a doctor for certain diseases, for the prevention of diseases or in cases of deficiency.

- From a legal perspective, food supplements are considered food. Unlike medical drugs, food supplements are not subject to an official approval process.

How do bolus doses of vitamin D and K enter the body?



High bolus doses of vitamins D and K2 are taken **orally**, for example by taking a high-dose food supplement.

Is there a recommended daily guidance value?

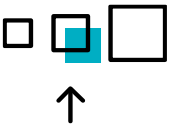
The tolerable upper intake level (UL) for vitamin D from all sources is **100 micrograms (µg) per day** for adults. This amount can be taken daily for a lifetime without any health impairments.

However, the tolerable upper intake level **does not apply** to high bolus doses, as these should not be taken daily, but at intervals of several days or weeks.

Is there a health risk?

Several studies found that vitamin D levels in the blood that can be achieved by administering high bolus doses were associated with an increased risk of health impairments.

What is the quality of the data?



The quality of the data is **moderate**. Some important data is missing or contradictory. For example, there is a lack of evidence on the combined bolus administration of vitamin D and vitamin K2. Furthermore, not all commercially available specific dosages of vitamin D and K2 have been studied scientifically.

How can the health risk posed by vitamin D and K2 supplements be reduced?

The BfR has developed maximum intake recommendations for vitamin D and vitamin K2 (as well as for all other vitamins and minerals) that can be used as a basis for **legal** maximum intake levels. The European Commission is currently developing EU-wide maximum intake levels for vitamins and minerals in food supplements and enriched food.

Manufacturers can already take the BfR recommendations for maximum levels of vitamins in food supplements into account.

Food supplements containing vitamin K should carry a warning stating that people taking anticoagulant medication should seek medical advice before taking them.

Consumers can refrain from taking food supplements with high bolus doses of vitamin D. If necessary, the BfR recommends taking a lower-dose preparation daily (recommended maximum amount in food supplements: 20 µg vitamin D per daily dose).

Patients taking oral anticoagulants of the coumarin type (vitamin K antagonistic) are advised to keep their vitamin K intake as constant as possible and to only use food supplements containing vitamin K under medical supervision.

1 Subject of the assessment

In this opinion, the German Federal Institute for Risk Assessment (BfR) has examined whether the intake of food supplements containing high bolus doses of vitamin D, including in combination with high doses of vitamin K2, at longer intervals poses any health risks. Various doses of commercially available products were assessed:

1. Vitamin D3 with a recommended intake of 175 µg every 7 days.

2. Vitamin D3 + vitamin K2 in combination as a bolus dose with a recommended intake of 250 µg vitamin D3 and 200 µg vitamin K2 every 10 days.

3. Vitamin D3 + vitamin K2 in combination as a bolus dose with a recommended intake of 500 µg vitamin D3 and 200 µg vitamin K2 every 20 days.

2 Result

Vitamin D supplements are available for daily use, but there are also supplements that are intended to be taken in high doses as a bolus at weekly, monthly or other intervals. Several studies have investigated the efficacy of daily vitamin D doses compared to bolus doses in terms of maintaining optimal vitamin D levels and health endpoints. However, the results are inconsistent and depend on the population studied and the respective dosage regimen.

With regard to the dosages and intake regimens assessed, it can be stated that no studies could be identified in which the health effects of 175 µg vitamin D every seven days or 250 or 500 µg vitamin D and 200 µg vitamin K2 were investigated with the intended intake intervals of 10 or 20 days. For the risk assessment, pharmacokinetic aspects of vitamin D metabolism and results from human studies in which bolus doses of vitamin D were given at intervals that were relatively close to those evaluated here were therefore used. The following conclusions can be drawn from these studies, although there is uncertainty as to whether the health effects derived from them would also be induced by the dosages and time intervals of intake assessed here:

Taking into account a half-life of the vitamin D storage form 25-hydroxyvitamin D (25-OH-D) of more than 20 days, a bolus dose of **500 µg (20,000 IU) vitamin D3 every 20 days** in individuals who are more than adequately supplied with vitamin D, i.e. who have 25-OH-D levels above 70 nmol/l or 28 ng/ml, could contribute to an increase in 25-OH-D serum levels to around100 nanomoles (nmol)/litre (l) (40 nanograms (ng)/ml). Serum levels of 25-OH-D above 100 nmol/l were associated with negative health effects and increased overall mortality in intervention and observational studies.

Taking **250 µg (10,000 IU)** of **vitamin D every 10 days or 175 µg (7,000 IU) of vitamin D every 7 days** would, with a high probability, not result in serum levels of 100 nmol/l (40 ng/ml). Therefore, these dosage/intake regimens carry a lower risk of adverse health effects, such as the occurrence of hypercalcaemia.

Regardless of the intake intervals, high bolus doses of vitamin D are expected to cause significant fluctuations in the serum levels of the parent substance cholecalciferol, which may be associated with undesirable effects such as the impairment of the induction of immunologically active substances.

There is currently no information available on the health effects that could result from a combined bolus dose of vitamin D and 200 µg vitamin K2. Even though the available studies suggest that vitamin K2 poses a low health risk to the general healthy population, vitamin K2 is approximately 3.5 times more potent than vitamin K1 in attenuating the therapeutic effect of oral anticoagulants of the coumarin type (vitamin K antagonists). Patients undergoing such drug therapy are advised to keep their vitamin K intake as constant as possible and to use food supplements containing vitamin K only under medical supervision. In particular, large fluctuations in vitamin K intake – such as those that would occur with a food supplement containing 200 µg of vitamin K2 every 10 or 20 days – therefore pose a high health risk for this group of people. To reduce this risk, the BfR recommends a maximum daily intake of 25 µg of vitamin K2 in food supplements (for persons aged 15 and over). Food supplements containing vitamin K should also carry a warning stating that persons taking anticoagulant medication should seek medical advice before taking them.

Further studies are needed to investigate the (long-term) effects of supplements containing vitamin K2 in the form of menaquinone 7 (MK-7) in healthy individuals, either alone or in combination with vitamin D. In particular, further clinical data on the interaction of vitamin D and vitamin K2 or MK-7 in metabolism is urgently needed before a reliable risk assessment of the combination of high-dose vitamin D and vitamin K2 can be carried out.

Finally, it should be noted here that food supplements that are to be taken at intermittent intervals carry a high risk of misuse. Depending on the dose and the interval between doses, misuse of the products is associated with a high risk of serious adverse health effects. In the opinion of the BfR, bolus doses of vitamin D and K2 should only be taken on medical advice and under medical supervision. This appears difficult to implement with food supplements, which is why the products, especially the highest-dose product (500 µg (20,000 IU) vitamin D3 every 20 days), pose a high health risk due to the possibility of misuse.

3 Rationale

3.1 Risk assessment

3.1.1 Hazard identification

3.1.1.1 Vitamin D

Vitamin D refers to a group of over 50 metabolites that are formed from cholesterol via a complex cascade of enzymatic and non-enzymatic reactions (Alonso et al., 2023). The individual metabolites differ greatly in their plasma concentrations and biological activities. Cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) are the two main forms of vitamin D. Vitamin D3 is mainly synthesised in human skin under the influence of sunlight or comes from animal sources such as fatty fish or egg yolk. In contrast, vitamin D2 is obtained exclusively from plant-based foods such as mushrooms. Overall, the usual nutrition contributes only 10 to 20 % of the human vitamin D supply (Holick, 2007; Linseisen et al., 2011). Higher intake amounts are possible through dietary supplements.

Vitamin D consumed through food is absorbed in the small intestine, incorporated into chylomicrons and released into the bloodstream via the lymphatic system. As a fat-soluble vitamin, vitamin D can be stored in fat cells and released again. In the bloodstream, vitamin D3 (cholecalciferol) and D2 (ergocalciferol) bind to vitamin D-binding protein (VDBP) and are transported to the liver. There, they are hydroxylated by the cytochrome P450 enzymes CYP2R1 (microsomal) and CYP27A1 (mitochondrial) at carbon atom 25, forming 25-hydroxyvitamin D (25-OH-D) – also known as calcidiol (Alonso et al., 2023), which is also bound to VDBP. 25-OH-D is the most common metabolite in the body, which is considered to be the storage form of vitamin D and is the precursor of biologically active vitamin D (1α,25-(OH)2-D) – also known as calcitriol. The 1α,25-(OH)2-D produced in the kidney acts as an endocrine modulator of calcium homeostasis (Prentice et al., 2008). This active metabolite increases serum calcium levels by increasing calcium absorption from the small intestine, reducing shedding from the kidneys and mobilising calcium from the bones (DiGirolamo et al., 2012; Holick, 2007).

However, cholecalciferol is transported not only to the liver but to all body tissue. The intake of cholecalciferol into various cell types is thought to be easier than that of 25-OH-D, as cholecalciferol is less strongly bound to VDBP (Hollis and Wagner, 2013). In addition, most

tissue contains both 25-hydroxylase and 1α-hydroxylase, so that the active metabolite 1α,25-(OH)2-D can also be produced extra-renally, where it acts mainly autocrinally or paracrinally and generally does not enter circulation (Alonso et al., 2023; Hansdottir et al., 2008; Hollis and Wagner, 2013; Prentice et al., 2008). There is evidence that the induction of some immunologically effective substances, such as cathelicidins[1] , may depend on the regular intake of absorbable cholecalciferol (Hollis and Wagner, 2013; Mazess et al., 2022).

3.1.1.2 Vitamin K2

According to Annex II of EU Regulation (EC) No. 1925/2006, food, including food supplements, may contain, in addition to vitamin K1, a specific vitamin K2 preparation obtained from *Bacillus subtilis natto*, which was assessed by EFSA in 2008 as part of the novel food procedure (see also 3.1.2.2).

Vitamin K2 is therefore only permitted in the EU in the form specified in European Commission Decision 2009/345/EC[2].

3.1.1.3 Synergistic effects of vitamin D3 and vitamin K2

Synergistic effects of vitamin D and K2 result from the fact that both fat-soluble vitamins play a central role in maintaining calcium homeostasis and bone mineralisation. Increased carboxylation of osteocalcin by vitamin K promotes the incorporation of calcium into the bones, while vitamin K-dependent carboxylation of matrix GLA protein binds calcium in the blood vessels. Vitamin D thus increases serum calcium levels, while vitamin K promotes the flow of calcium from the serum into the bones (Gröber and Kisters, 2018). Due to the synergistic effects of vitamins D3 and K2, the two vitamins are often used together in food supplements.

3.1.2 Hazard characterisation

3.1.2.1 Vitamin D

Vitamin D when taken daily

The health effects of high or excessive vitamin D intake through daily supplementation have already been discussed in detail in BfR Opinion 065/2023 of 7 December 2023 (BfR, 2023). This statement also pointed out that EFSA updated its risk assessment and derived a *tolerable upper intake level* (UL) for vitamin D in 2023 (EFSA, 2023). While the EFSA assessment from 2012 used hypercalcaemia as an indicator of vitamin D toxicity to derive a UL for vitamin D (EFSA, 2012), the current assessment also takes hypercalciuria into account, as this indicates excessive vitamin D intake earlier than hypercalcaemia (EFSA, 2023).

The current EFSA opinion was not able to identify any No Observed Adverse Effect Level (NOAEL), only a Lowest Observed Adverse Effect Level (LOAEL) based on two studies in which daily administration of 250 µg vitamin D in combination with calcium over one or three years led to persistent hypercalciuria (Aloia et al., 2018; Billington et al., 2020, both

[1] Cathelicidins are antimicrobial peptides secreted by epithelial and immune cells (Burkes et al.; 2019).
[2] 2009/345/EC: Commission Decision of 22 April 2009 authorising the placing on the market of Vitamin K2 (menaquinone) from Bacillus subtilis natto as a novel food ingredient under Regulation (EC) No 258/97 of the European Parliament and of the Council (https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32009D0345)

cited in: EFSA, 2023). As no NOAEL could be identified, the UL was derived using an uncertainty factor of 2.5.

For adults, including pregnant and breastfeeding women, as well as for children and adolescents aged 11 to 17, the UL was set at 100 µg (4,000 IU) per day, and for children aged 1 to 10, at 50 µg (2,000 IU) per day. For infants under six months of age, the EFSA derived a UL of 25 µg (1,000 IU) per day and for infants aged seven to under twelve months, a UL of 35 µg (1,400 IU) per day (EFSA, 2023). The current EFSA ULs remain therefore unchanged from those in 2012.

By definition, the UL describes the amount of a micronutrient that can be consumed daily from all sources for a lifetime without causing any adverse health effects (https://www.efsa.europa.eu/de/glossary/tolerable-upper-intake-level). The UL is therefore not applicable to bolus doses of vitamin D.

Pharmacokinetics of vitamin D after bolus administration

a) 25-hydroxyvitamin D (25-OH-D)

25-OH-D is the storage form of vitamin D in the body and is produced in the liver (Alonso et al., 2023). Due to its relatively high serum concentration in the nanomolar region and the long half-life of 25-OH-D (10 to 40 days) (Datta et al., 2017; Jones et al., 2014b), 25-OH-D is also considered a robust biomarker for determining vitamin D status (Alonso et al., 2023). However, the half-life can vary greatly from person to person (Datta et al., 2017; Jones et al., 2014b).

High bolus doses of vitamin D lead to a rapid increase in 25-OH-D levels, which can reach values > 75 nmol/l in the first few weeks, depending on the basal serum concentration and the dose. However, the increase is only temporary with single doses and levels usually return to baseline after about three months.

Intermittent vitamin D administration at intervals of three or more months can lead to significant fluctuations in 25-OH-D levels. In contrast, daily vitamin D administration leads to a gradual and continuous increase in 25-OH-D levels without major fluctuations (Kearns et al., 2023; Ketha et al., 2018; Romagnoli et al., 2008; Vidal et al., 2024).

b) Cholecalciferol (vitamin D3)

After a bolus dose of cholecalciferol, the concentration of cholecalciferol in serum rises very steeply within a day and then falls rapidly again due to its short half-life of about 20 hours (Ketha et al., 2018; Mazess et al., 2021).

Due to the short half-life of cholecalciferol, even weekly bolus doses of vitamin D would lead to significant fluctuations in serum cholecalciferol concentration.

c) 1α,25-dihydroxyvitamin D (1α,25-(OH)2-D)

Only in the kidney is 25-OH-D metabolised by 1α-hydroxylase CYP27B1 into the active form calcitriol (1α,25-dihydroxyvitamin D; 1α,25-(OH)2-D) (Jones et al., 2014a).

At four to six hours, the half-life of 1α,25-(OH)2-D is very short. Under physiological conditions, however, serum levels of 1α,25-(OH)2-D remain largely constant due to the strict regulation of calcium and phosphate homeostasis (Latic and Erben, 2021).

d) 24,25-dihydroxyvitamin D (24,25(OH)2-D)

An important component of the homeostatic control of serum calcium levels is the catabolism of 25-OH-D (Herrmann, 2023) to replace excessive serum levels of the active metabolite 1α,25-(OH)2-D. The breakdown of 25-OH-D is induced by 24-hydroxylation via CYP24A1, which leads to the formation of the inactive vitamin D metabolite 24,25(OH)2-D.

High bolus doses of vitamin D (as well as high daily intakes) and the resulting rapid increase in 25-OH-D can also lead to a sustained increase in 24-hydroxylase CYP24A1 activity over several months, with equally long-lasting elevated 24,25(OH)2-D concentrations (Ketha et al., 2018; Owens et al., 2017). This ultimately leads to a reduction in the previously increased active metabolite 1α,25-(OH)2-D (Owens et al., 2017).

In a study by Owens et al. (2017), 46 male athletes were administered either 35,000 IU (875 µ) or 70,000 IU (1,750 µg) of vitamin D per week over a period of 12 weeks. After discontinuing the vitamin supplements, the athletes were observed for a further six weeks. In the 35,000 IU group, 25-OH-D levels rose from 85 nmol/l (34 ng/ml) to 108 nmol/l (43 ng/ml) after six weeks and in the 70,000 IU group from 86 nmol/l (34 ng/ml) to 122 nmol/l (49 ng/ml). In week 12, the 25-OH-D level in the high-dose group was on average 10 % to 15% higher than in the group that had received the lower dose. In both groups, a significant increase in 24,25(OH)2-D concentration was observed in the sixth week, which continued to rise and led to an increase of 2.4% in the 70,000 IU group compared to 0.4 % in the 35,000 IU group by week 12. The increased 24,25(OH)2D level persisted for six weeks after discontinuation of vitamin D supplementation, suggesting long-term induction of 24-hydroxylase CYP24A1. Accordingly, serum levels of the previously elevated active metabolite 1α,25-(OH)2-D decreased again. The authors also speculate that 24,25(OH)2-D binds to the VDR and subsequently reduces the biological activity of 1α,25-(OH)2-D (Owens et al., 2017).

In another study involving 40 breastfeeding mothers, the effects of a single dose of 150,000 IU (3,750 µg) of vitamin D3 were compared with a daily dose of 5,000 IU (125 µg) over 28 days (identical cumulative dose, but administered daily) (Ketha et al., 2018). This study showed that the bolus dose led to significantly higher 25-OH-D concentrations in the first 15 days compared to daily intake. Within the first 3 days after bolus administration, the 25-OH-D concentration rose from an initial 73 nmol/l (29 ng/ml) to a maximum of 125 nmol/l (50 ng/ml) and then slowly declined again. After 28 days, the 25-OH-D concentrations in the bolus group were around 100 nmol/l (40 ng/ml) and in the other group around 107 nmol/l (43 ng/ml). Although there was little difference in 25-OH-D concentrations between the two groups after 28 days, differences were observed in the increase in 24,25(OH)2-D: After bolus administration, the concentration of 24,25(OH)2-D increased by approximately 50 %, and after daily administration by only approximately 30 %; the increased concentrations remained stable for at least 28 days (last measurement point) after vitamin D administration (Ketha et al., 2018).

The available data suggest that the availability of active 1α,25-(OH)2-D in individual tissue depends on the balance between activating 1α-hydroxylase (CYP27B1) and inactivating 24-hydroxylase (CYP24A1). A single megadose of vitamin D can disrupt this strict hormonal control and thus increase the risk of adverse effects (Vidal et al., 2024).

e) Fibroblast growth factor 23 (FGF23)

Fibroblast growth factor 23 (FGF23), which is mainly produced in osteoblasts and osteocytes in the bone, also plays an important role in phosphate and vitamin D homeostasis (Razzaque, 2022) by negatively regulating the formation of the active metabolite. FGF23 inhibits 1α-hydroxylase CYP27B1, resulting in less 1α,25-(OH)2-D being formed, and stimulates 24-hydroxylase CYP24A1, leading to the formation of the inactive metabolite 24,25(OH)2-D (Latic and Erben, 2021).

Increased expression of FGF23 can apparently be induced by high bolus doses of vitamin D, as the following studies show:

A study involving 45 participants with baseline vitamin D levels of 50 nmol/l (20 ng/ml) showed that a bolus of 300,000 IU (7,500 µg) of vitamin D2 increased both 1α,25-(OH)2-D and FGF23 concentrations (Turner et al., 2013).

In another study, 27 individuals with serum 25-OH-D levels below 75 nmol/l (30 ng/ml) were divided into three groups (Pepe et al., 2024) and supplemented with single doses of either 25,000 IU (625 µg), 600,000 IU (15,000 µg) of vitamin D or a placebo. After three days, the two intervention groups showed a significant increase in 25-OH-D levels from 30 nmol/l to 50 nmol/l (12 ng/ml to 20 ng/ml) in the 25,000 IU group and from 43 nmol/l to 148 nmol/l (17 ng/ml to 59 ng/ml) in the 600,000 IU group. In addition, an increase in 24,25(OH)2-D and FGF23 concentrations was observed in the 600,000 IU group, suggesting that the high single dose induced the catabolic metabolism of vitamin D via 24-hydroxylase CYP24A1 in order to avoid toxic effects. In contrast, neither 24,25(OH)2-D nor FGF23 were induced to a greater extent in the 25,000 IU group with final serum levels in the physiological region of 50 nmol/l (20 ng/ml) (Pepe et al., 2024).

Finally, Pallone et al. (2025) investigated the effects of vitamin D supplementation in patients with primary hyperparathyroidism (PHPT), i.e. primary hyperfunction of the parathyroid glands, compared to individuals who were not affected by this condition. All study participants received 14,000 IU (350 µg) per week for 12 weeks. Serum 25-OH-D levels rose from 55 nmol/l (22 ng/ml) to 80 nmol/l (32 ng/ml) in the PHPT group and from 50 nmol/l (20 ng/ml) to 83 nmol/l (33 ng/ml) in the non-PHPT group. In both groups, an increase in FGF23 concentration was observed after 12 weeks, suggesting that even at serum 25-OH-D levels below 100 nmol/l (40 ng/ml), inhibition of the active metabolite 1α,25-(OH)2-D may already be inhibited (Pallone et al., 2025).

A meta-analysis by Zittermann et al. (2021a and 2021b), which included randomised controlled trials, particularly with patients with end-stage renal or heart failure, also showed that vitamin D doses above 3,000 IU (> 75 µg) per day and 25-OH-D concentrations ≥ 100 nmol/l significantly increased FGF23 concentrations, whereas this was not observed with daily vitamin D doses ≤ 3000 IU (≤ 75 µg) and in studies with 25-OH-D concentrations < 100 nmol/l (Zittermann et al., 2021a; Zittermann et al., 2021b). It should be noted here that comparing FGF23 concentrations from different studies using different FGF23 assays has limitations because some assays measure intact FGF23 and others measure a combination of the intact molecule and an inactive C-terminal fragment (Mazess et al., 2021).

In summary, it can be said that the pharmacokinetics of bolus doses of vitamin D differ from those of moderate daily vitamin D intake, even at identical cumulative doses. For example, some studies have measured higher concentrations of the inactive metabolite 24,25(OH)2-D (Ketha et al., 2018; Owens et al., 2017; Pepe et al., 2024). It has also been observed that FGF23 is induced to a greater extent after high bolus doses (Pallone et al., 2025; Pepe et al.,

2024; Turner et al., 2013). The available data therefore suggest that, in contrast to moderate (daily) doses, high bolus doses of vitamin D tend to induce catabolic metabolism in order to replace high serum concentrations of the active metabolite 1α,25-(OH)2-D. At very high 25-OH-D levels, which can occur after high bolus doses, the strictly regulated calcium homeostasis may be overwhelmed in maintaining constant serum levels of the active metabolite, ultimately increasing the risk of hypercalcaemia.

Health effects of high vitamin D bolus doses

A double-blind randomised study involving 200 women and men aged 78 ± 5 years living in communal facilities who had previously suffered a fall investigated whether monthly high-dose vitamin D administration over 12 months led to a refinement in lower limb function (Bischoff-Ferrari et al., 2016). The intervention groups received either 60,000 IU (1,500 µg) or 24,000 IU (600 µg) of vitamin D with 300 µg of calcidiol (25-OH-D), and the control group received 24,000 IU (600 µg) of vitamin D. The mean initial 25-OH-D levels in the three groups ranged from 46 to 52 nmol/L (18 to 21 ng/ml). After 12 months of treatment, serum 25-OH-D levels in the 24,000 IU (control)group had risen to 76 nmol/L (30 ng/ml) and in the other two groups to 100 nmol/L (40 ng/ml) in the 60,000 group and to 111 nmol/L (44 ng/ml) in the 24,000/calcidiol group. Despite the much higher increases in serum concentrations to ≥ 100 nmol/l in the intervention groups compared to the control group (24,000 IU), the higher monthly vitamin D bolus doses (60,000 and 24,000 IU + calcidiol) did not lead to a refinement in lower limb function, but actually increased the frequency of falls (Bischoff-Ferrari et al., 2016).

In another double-blind, placebo-controlled study involving 2,256 women (≥ 70 years) living in community facilities, the researchers investigated whether a single annual dose of 500,000 IU (12,500 µg) of vitamin D administered once a year in autumn or winter over a period of 3 to 5 years reduces the risk of falls or fractures (Sanders et al., 2010). At the start of the study, serum 25-OH-D levels were between 40 and 65 nmol/l (16 and 26 ng/ml). One month after the intervention, serum 25-OH-D levels in the vitamin D group were measured at > 120 nmol/l (48 ng/ml), with 82 % of the study group having levels of 100 nmol/l (40 ng/ml) or higher and 24 % having levels of 150 nmol/l (60 ng/ml) or higher. After a further three months, the median 25-OH-D levels in the vitamin D group had fallen to around 90 nmol/l (36 ng/ml). In addition, it was found that in the group of women who had supplemented 500,000 IU (12,500 µg) of cholecalciferol annually, there was an occurrence of 15 % more falls and 26 % more fractures than in the placebo group, with most fractures not associated with a fall. A post-hoc analysis showed that the falls and, in most cases, the fractures in the vitamin D group occurred primarily in the first three months after the intervention and thus in a period when serum 25-OH-D levels were above 100 nmol/l (40 ng/ml) (Sanders et al., 2010).

Another double-blind, placebo-controlled study involving 9,440 elderly women and men (4,354 men and 5,086 women, aged ≥ 75 years) investigated whether a single annual dose of 300,000 IU (7,500 µg) of vitamin D_2(ergocalciferol) administered once a year in autumn or winter over a period of 3 years reduces the risk of fractures (Smith et al., 2007). In this study, too, no positive effect on the prevention of fractures was observed in the vitamin $D(_2)$ group. In contrast, a significantly increased risk of hip fractures was observed in women in the vitamin D group; this effect was not observed in men (Smith et al., 2007).

Finally, a double-blind, placebo-controlled study in Australia with 21,315 participants (aged 60 and older) investigated whether a monthly dose of 60,000 IU (1,500 µg) of vitamin D over 5 years reduces the risk of mortality (Neale et al., 2022). During follow-up, the mean 25-OH-D serum concentration was 77 nmol/l (31 ng/ml) in the placebo group and 115 nmol/l (46 ng/ml) in the vitamin D group (measured in 4,441 subjects). Overall mortality was not reduced in this study. Furthermore, in further analyses, without taking into account the first

two years of follow-up, a slightly increased risk of death from cancer (*hazard ratio* (HR) 1.24 [95 % confidence interval (CI): 1.01-1.54; p=0.05] (Neale et al., 2022).

The results show that long-term administration of high bolus doses of vitamin D may be associated with health risks. The increased risk of fractures observed in some studies could be due to the fact that bolus doses of ≥ 100,000 IU led to an acute increase in bone turnover markers (e.g. *C-terminal telopeptide of type I collagen* (CTX) or cross-linked *N-telopeptide* from type I collagen (sNTX). For example, a single dose of 600,000 IU resulted in elevated CTX concentrations for two months (Bowles et al., 2024; Rossini et al., 2012a; Rossini et al., 2012b). Such an increase in bone turnover markers indicates increased bone resorption, which can have a negative impact on bone health.

In addition to the potentially harmful effects of very high bolus doses of vitamin D, other studies have found no negative effects, but also no benefits, from supplementation with high bolus doses (Jolliffe et al., 2021; Martineau et al., 2017). A lack of benefit can also pose a health risk if the supply status of deficient individuals is not improved.

3.1.2.2 Vitamin K2

With regard to possible health risks associated with vitamin K2 supplementation in the form of menaquinone 7 (MK-7), we refer to the BfR opinion 065/2023 “High-dose vitamin D food supplements can cause long-term health impairment” [1]. This statement concluded that, in the human studies available to date, no negative health effects were observed with MK-7 supplementation in doses of up to approximately 400 µg/day. Furthermore, taking into account the overall scientific evidence available, there was/is no evidence of adverse health effects from taking food supplements with daily doses of 200 µg MK-7 in healthy adults (the BfR, 2023).

However, it is known that vitamin K2 can weaken the therapeutic effect of coumarin-type anticoagulants by a factor of about 3.5 compared to vitamin K1. The BfR therefore recommends that products containing vitamin K should always carry a warning label for people who use coumarin-type anticoagulants (BfR, 2021).

EFSA has not yet carried out a generic risk assessment of vitamin K2 or the various isoforms of vitamin K2 used for supplementation. However, in 2008, as part of the novel food procedure, the EFSA conducted an assessment of the safety and bioavailability of vitamin K2 from a menaquinone-rich oil based on *Bacillus subtilis ssp. natto,* which contains a mixture of MK-7 with a lower proportion of MK-6. According to the application at that time, the oil was to be used to enrich conventional food, including food supplements, and food for special nutritional purposes intended for the general population (EFSA, 2008). In its risk assessment, the EFSA concluded that vitamin K from the menaquinone-rich oil had bioavailability and was safe for human consumption at the levels requested (EFSA, 2008). Based on the applicant's information on the intended use of MK-7, a conservative estimate of the average daily intake of MK-7 was 36 µg (adult women) to 54 µg (male teenagers) or, in high intake percentiles, 75 µg (children) to 115 µg (male teenagers) (EFSA, 2008) and derived that adult women and men consuming average amounts of enriched food and food supplements with an average daily dose of MK-7 of 50 µg would consume a total of 86 to 95 µg or 1.4 to 1.6 µg/kg body weight (BW) per day and, in high intake percentiles, 131 to 157 µg/day or 2.2 to 2.6 µg/kg BW/day. These intake levels of MK-7 were considered safe by EFSA (EFSA, 2008).

3.1.3 Exposure

3.1.3.1 Vitamin D

Human exposure to vitamin D results from the duration of irradiation of the skin with UVB radiation and the consumption of food or vitamin D supplements. Intake from a typical diet and possible intake from enriched food, novel food products and food supplements has already been discussed in detail in the BfR opinion issued 7 December 2023 (BfR, 2023). According to this, the intake of vitamin D from a typical diet is in the region of only about 5 to 10 µg per day.

According to the assessment of the Joint Expert Commission on the Classification of Substances of the BVL and BfArM (2017), taking into account risk groups and fluctuations due to endogenous synthesis, an amount of up to 20 µg/day may be rationalised in the context of diet and food supplements. However, from the Commission's point of view, a dosage of more than 20 µg/day does not necessarily lead to classification as a medical drug (BVL and BfArM, 2017).

The dosages and intake recommendations assessed here of 7,000 IU (175 µg), 10,000 IU (250 µg) and 20,000 IU (500 µg) every 7, 10 or 20 days would, in purely mathematical terms, result in daily doses of 1000 IU (25 µg) of vitamin D – and thus only slightly above the dose that the above-mentioned expert commission considered to be a suitable dose with nutritional or physiological effects in the context of nutrition/food supplements. However, as described above, the kinetics of bolus doses are not comparable to those of moderate daily doses, so that no statement can be made about the actual exposure to vitamin D from the above-mentioned dosages.

3.1.3.2 Vitamin K2

There is uncertainty about the vitamin K2 concentration in food and thus also about the intake of vitamin K2 from a typical diet. There is also uncertainty about the physiological requirement and the normal range of serum concentrations, including depending on the age, sex and health status of the population.

The available data (see also BfR Opinion 065/2023) suggest that in Germany (and other countries in Europe), only very small amounts of MK-7 are consumed through conventional food (the median intake for men in the EPIC Heidelberg cohort was 0.8 µg/day) (Nimptsch et al., 2008).

Dietary supplement doses of 50 µg vitamin K2 as MK-7 were considered as daily doses by EFSA in its exposure assessment carried out in 2008 as part of the novel food evaluation (EFSA, 2008). The dose of 200 µg MK-7 contained in some food supplements would be four times higher on the day of intake, but would only be taken every 10 or 20 days. Therefore, the dosages cannot be compared with a typical daily dose.

Since the half-life of MK-7 is approximately 3 days (Schurgers et al., 2007), it must be assumed that the administration of 200 µg MK-7 every 10 days or every 20 days will not result in constant serum levels, but rather in fluctuations of MK-7 in the serum. However, to the BfR's knowledge, there are no studies investigating the effects of corresponding dosages and intake regimens on vitamin K status and health endpoints.

3.1.4 Risk characterisation

As no studies could be identified in which the effects of the dosages and intake intervals of vitamin D assessed here, including in combination with vitamin K2, were investigated, an assessment is made below based on knowledge of the kinetics of vitamin D metabolism and studies with similarly high dosages and intake intervals as those considered here.

3.1.4.1 Vitamin D as a bolus dose of 175 µg (7,000 IU) every 7 days

When taking a preparation with a recommended intake of 175 µg vitamin D3 every 7 days as intended, the BfR does not expect any fluctuations in 25-OH-D levels. However, due to the short half-life of cholecalciferol, fluctuations in cholecalciferol concentrations are to be expected.

The vitamin D dose used in a double-blind, placebo-controlled intervention study by Lips et al. (2010) is closest to the doses for assessment and is therefore used here. The study investigated the extent to which a weekly dose of 8,400 IU (210 µg) of vitamin D affects stability and muscle strength in 226 people aged ≥ 70 years with a baseline 25-OH-D level below 50 nmol/l (20 ng/ml). Supplementation was carried out over 16 weeks. The 25-OH-D levels in the vitamin D arm rose on average from 35 nmol/l (14 ng/ml) to 65 nmol/l (26 ng/ml). Vitamin D supplementation had no positive effect on physical instability, but was also not associated with adverse effects such as hypercalcaemia (Lips et al., 2010).

Although this study only included individuals with baseline 25-OH-D levels below 50 nmol/l (20 ng/ml), a higher dose than the one being assessed here was administered. Since 25-OH-D levels remained below 100 nmol/l, an increase in 25-OH-D levels to 100 nmol/l is not to be expected with the dosage regimen under assessment. No reliable assessment can be made as to whether 175 µg of vitamin D3 every 7 days could induce 24-hydroxylase (CYP24A1).

3.1.4.2 Vitamin D3 as a bolus dose of 250 µg (10,000 IU) every 10 days

When used as intended, preparations containing 250 µg (10,000 IU) every 10 days are not expected to cause fluctuations in 25-OH-D levels after an initial peak due to the long half-life of 25-OH-D (10 to 40 days). However, fluctuations in cholecalciferol concentrations may also occur with this product due to the short half-life of cholecalciferol.

No studies are available for this dosing regimen either, which is why no clear statements can be made about the possible resulting 25-OH-D and cholecalciferol concentrations. Nor is it possible to say whether or under what conditions 24-hydroxylase (CYP24A1) induction could occur.

Only one study with a similar dosage regimen was identified. Therein, 1,300 children and adolescents aged 3 to 15 years were given either 14,000 IU (350 µg) or a placebo weekly for 8 months (Loeb et al., 2019). The baseline 25-OH-D values averaged 65 nmol/l (26 ng/ml) at the start of the study and rose to 92 nmol/l (37 ng/ml) in the vitamin D arm. No adverse effects were observed.

In this study, despite a higher dosage, a shorter intermittent interval of intake and high 25-OH-D baseline values (65 nmol/l), no serum values above 100 nmol/l (40 ng/ml) were achieved in comparison to the dosage regimen under evaluation. It can therefore be

assumed that even when taking 250 µg (10,000 IU) every 10 days, serum 25-OH-D levels will not exceed 100 nmol/l (40 ng/ml).

3.1.4.3 Vitamin D3 as a bolus dose of 500 µg (20,000 IU) every 20 days

When used as intended, an initial peak in 25-OH-D levels is to be expected according to pharmacokinetics. With regular intake, 25-OH-D levels may fluctuate in individuals with a shorter half-life of 25-OH-D (e.g. 10 days), while 25-OH-D levels in individuals with longer half-lives of 25-OH-D (e.g. 40 days) are likely to stabilise at a constant level. Due to the short half-life of cholecalciferol (20 hours), extreme fluctuations in cholecalciferol levels must be expected.

Two studies were identified in which 20,000 IU (500 µg) of vitamin D was administered weekly and which are therefore most comparable to the dosage for assessment here:

One of the two studies was a placebo-controlled intervention study in which 34 healthy adults aged 18 to 52 were given 20,000 IU (500 µg) of cholecalciferol or an identical placebo weekly for 17 weeks (Simpson et al., 2015). The primary endpoint was the occurrence of acute infection; secondary endpoints were duration and severity of infection, and tertiary endpoints were changes in serum 25-hydroxyvitamin D (25-OH-D) levels and adverse effects. Serum 25-OH-D levels rose on average from an initial 68 nmol/l (27 ng/ml) to 101 nmol/L (40 ng/ml), with the baseline value being significantly lower in those treated with vitamin D than in those receiving a placebo (60.5 vs. 76.4, p = 0.040). No adverse effects such as hypercalcaemia were observed (Simpson et al., 2015). However, this was a pilot study with a very small study group and a short intervention period.

In the other study, 265 residents (mean age: 85 years) in nursing homes in Canada were given weekly doses of 20,000 IU (500 µg) of vitamin D (Feldman et al., 2014). Among those (n = 147) who had received this dose weekly for at least six months or longer (17 % of the group had also taken 400 IU (10 µg) of vitamin D daily), the mean 25-OH-D level rose to 112 nmol/l (45 ng/ml). The lowest 25-OH-D level was 57 nmol/l, the highest 187 nmol/l. Hypercalcaemia (> 2.6 mmol/l) was diagnosed in 14 % of the study group, but this was not associated with higher 25-OH-D concentrations. No baseline vitamin D levels were measured in this study (Feldman et al., 2014).

It can be derived from the two studies that a dose of 20,000 IU (500 µg) of vitamin D per week has the potential to increase serum 25-OH-D levels to above 100 nmol/l (40 ng/ml) in individuals with high nutritional status (Simpson et al., 2015). It cannot be ruled out that the same dose every 20 days has the same potential in individuals with high serum levels > 70 nmol/l (28 ng/ml) and a 25-OH-D half-life > 20 days (on average, this is 10 to 40 days).

In summary, it can be said that the assessed bolus doses of vitamin D from dietary supplements are significantly lower than the doses used in studies (annual bolus dose of ≥ 300,000 IU or monthly dose of 60,000 IU), in which negative health effects such as increased falls and fractures and a slightly increased risk of mortality were observed (Bischoff-Ferrari et al., 2016; Neale et al., 2022; Sanders et al., 2010; Smith et al., 2007). However, as no studies could be identified with the dosages and corresponding intake intervals in question, it is not possible to make a reliable health risk assessment in this regard.

Taking into account studies that are only partially comparable (Feldman et al., 2014; Simpson et al., 2015), it can be assumed that in individuals with high basal 25-OH-D levels > 70 nmol/l (28 ng/ml) and an individual 25-OH-D half-life > 20 days (the average is 10 to 40

days) can achieve 25-OH-D serum concentrations of around 100 nmol/l (40 ng/ml) by taking 500 µg (20,000 IU) of vitamin D3 as a bolus every 20 days.

In intervention studies, 25-OH-D serum levels ≥ 100 nmol/l (40 ng/ml) were associated with an increased risk of hypercalcaemia, falls, fractures and a slightly increased risk of dying from cancer (Zittermann et al., 2017; Michos et al., 2022; Neale et al., 2022; Sanders et al., 2010; Bischoff-Ferrari et al., 2016). In observational studies, 25-OH-D levels above 75 to 100 nmol/l (> 30 to 40 ng/ml) with increased overall mortality (Durup et al., 2012; Melamed et al., 2008; Sempos et al., 2013), cardiovascular disease and cardiovascular mortality (Aleksova et al., 2016; Durup et al., 2015; Wang et al., 2019; Zhang et al., 2017), fractures (Bleicher et al., 2014; Julian et al., 2016) and frailty (Ensrud et al., 2011; Ensrud et al., 2010; Kojima et al., 2017). Although no causal relationships can be derived from observational studies, the results of these studies suggest that serum 25-OH-D levels above 75 to 100 nmol/l may be associated with an increased health risk.

In addition, taking vitamin D supplements in the aforementioned dosages over a period of 20 days results in fluctuations in cholecalciferol concentration, which can lead to fluctuations in the extra-renal production of the active metabolite 1α,25-(OH)2-D. This could also lead to an impairment of autocrine function, such as the induction of immunologically effective substances (Hollis and Wagner, 2013; Mazess et al., 2022).

Taking dietary supplements containing 250 µg (10,000 IU) every 10 days or 175 µg (7,000 IU) every 7 days does not have a probability of reaching serum levels of 100 nmol/l (40 ng/ml). Therefore, the risk of adverse effects, such as hypercalcaemia, appears to be relatively low at these dosages. However, fluctuating cholecalciferol levels could influence the expression of immunologically effective substances, for example, which may also be considered undesirable.

3.1.4.4 Combined administration of vitamin D3 and vitamin K2

There are currently very few studies available for a health risk assessment of preparations with combined doses of vitamin D3 and vitamin K2 (as MK-7). The supplements administered in the studies contained doses of 10 to 90 µg of vitamin D and 50 to 720 µg of MK-7 per day (Aguayo-Ruiz et al., 2020; Kannellakis et al., 2012; Diederichsen et al., 2022; Zhang et al., 2020; Kurnatowska et al., 2015; Rønn et al., 2016). Some of the products also contained calcium (500 or 800 mg per daily dose).

Most of the studies were conducted with the aim of investigating positive effects on bone density or the carboxylation of vitamin K-dependent proteins. None of the studies identified aimed to investigate the safety of supplementation; nor were any adverse effects reported or observed. Only one of the studies (Zhang et al., 2020) was conducted with healthy older men and healthy postmenopausal women; the other studies involved patients who had undergone lung, kidney or heart transplants, patients with chronic kidney disease and dialysis patients with type 2 diabetes or coronary heart disease, as well as postmenopausal women with osteopenia. The studies were also conducted with relatively small groups and mostly only short follow-up periods. It is therefore unclear whether the results are transmissible to the healthy general population. Since the vitamin D doses in the studies were relatively low (< 100 µg/day) and were administered daily rather than as a bolus, the results cannot be compared with the doses and intake regimens to be evaluated here.

Given the existing gaps in knowledge, it is not possible to make a conclusive risk assessment of the health effects of supplementing 200 µg of vitamin K2 in the form of MK-7 in combination with high doses of vitamin D (250 µg or 500 µg) every 10 or 20 days.

Even though the available studies suggest that vitamin K2 poses a low health risk to the general healthy population, it is known that vitamin K2 is approximately 3.5 times more potent than vitamin K1 in attenuating the therapeutic effect of oral coumarin-type anticoagulants (vitamin K antagonists). Patients undergoing such drug therapy are advised to keep their vitamin K intake as constant as possible and to use vitamin K-containing food supplements only under medical supervision. The fluctuations in vitamin K intake that would be expected from a food supplement containing 200 µg of vitamin K2 every 10 or 20 days therefore pose a high health risk for patients undergoing therapy with vitamin K antagonistic. To reduce this risk, the BfR recommends a maximum daily intake of 25 µg of vitamin K2 in food supplements (for persons aged 15 and over). The BfR also believes that food supplements containing vitamin K should always carry a warning stating that people taking anticoagulant medication should seek medical advice before taking them (BfR, 2021).

3.1.5 Other aspects

3.1.5.1 Consumer behaviour – improper use

The rationale for the use of megadoses in the form of single or intermittent bolus doses is based, among other things, on the assumption that this will improve compliance with the set therapeutic goals compared to daily doses (Rothen et al., 2020; Vidal et al., 2024). In general, high-dose vitamin D supplements are therefore medical drugs that are taken under medical supervision. Food supplements with high doses of vitamin D that are to be taken independently as a bolus have not been common practice to date.

However, products with the dosages assessed here are commercially available and marketed as food supplements. With regard to the intake intervals specified on the products, the BfR considers the 20-day and 10-day intake intervals to be particularly difficult to implement, as no simple system for intake can be derived from them. It cannot be ruled out that such a product may be taken again before the 10 or 20 days have elapsed. From a health perspective, this is particularly critical in the case of a dose of 500 µg (20,000 IU) every 20 days, as certain individuals (high 25-OH-D serum levels, long 25-OH-D half-life) could achieve 25-OH-D serum levels of over 100 nmol/l (40 ng/ml) even when taking the product according to the manufacturer's recommendations. Shorter intervals between doses would further increase the risk of a corresponding rise in serum 25-OH-D levels.

In principle, it cannot be ruled out that consumers may even take products that are intended to be taken as bolus doses at specific intervals on a daily basis, as daily intake is common for food supplements. Daily intake would lead to a significant exceedance of the UL for all three dosages considered here. It should be noted that even a slight long-term exceedance of the UL can lead to negative health effects, such as hypercalcaemia (the BfR, 2023; Zittermann et al., 2023). In the case of persistent hypercalcaemia, this can lead to kidney stones, kidney calcification and ultimately to a decrease in kidney function (the BfR, 2023).

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