BfR

Bundesinstitut für Risikobewertung

Vitamin D: consumption of high-dose food supplements is unnecessary

BfR Opinion No 035/2020 issued 31 July 2020

The German Federal Institute for Risk Assessment (BfR) has prepared a health risk assessment for products sold on the market as food supplements containing a daily dose of chole-calciferol—the precursor to active vitamin D—of 50 or 100 micrograms. These products are representative of certain high-dose preparations used by some consumers to increase their intake of vitamin D.

In humans, vitamin D is formed in the skin following its exposure to sunlight. In comparison to the body's own formation of vitamin D, dietary consumption generally makes up only a relatively small proportion of the vitamin D supply to the body. While an overdose resulting from the body's own production is not possible, it certainly can result from the consumption of high doses of vitamin D—such as via certain food supplements.

An overdose of this kind leads to elevated calcium values in blood serum (hypercalcaemia). The clinical symptoms associated with hypercalcaemia in humans range from fatigue and muscular weakness to vomiting and constipation, and can even lead to cardiac arrhythmias and the calcification of blood vessels. If persistent, hypercalcaemia can lead to kidney stones, kidney calcification and, ultimately, to a loss of renal function.

Even without exposure to sunlight, a daily consumption of 20 µg of vitamin D is adequate to meet the body's needs for this vitamin for the vast majority (97.5%) of the population.

The European Food Safety Authority (EFSA) has set a UL value (tolerable upper intake level) of 100 µg for vitamin D. According to the latest scientific research, if adults and children aged eleven and older consume a daily quantity of no more than 100 µg, any impairments to health are unlikely. This UL value includes the intake of vitamin D from all sources, and thus includes intake from supplements, normal dietary intake and intake from food that has been fortified with vitamin D. If high-dose vitamin D preparations are also consumed, this figure may be exceeded in combination with other sources of the vitamin.

From the perspective of nutritional science, the daily consumption of vitamin D preparations containing a 50 µg or 100 µg dose is not necessary. On the other hand, the BfR considers it unlikely that impairments to health will result from the occasional consumption of such high-dose preparations. If such high-dose vitamin D products are consumed on a daily basis over a longer period of time, however, the latest research does point to an elevated risk to health.

The BfR notes that, given an adequate length of time spent outdoors with corresponding exposure of the skin to sunlight, plus a balanced diet, an adequate supply of Vitamin D can be achieved by individuals without having to take vitamin D preparations. Individuals in risk groups for which a serious lack of vitamin D or a vitamin deficiency requiring medical intervention may be more likely to occur, should first clarify any need to take such preparations with their attending physician or general practitioner.

This opinion does not constitute a decision as to whether or not a product should be classified as a foodstuff, nor should it be interpreted as such.

BfR risk profile: Regular consumption of high-dose vitamin D food supplements (Opinion no. 035/2020)				
A Affected persons	General population			
B Probability Of an impairment to health following regular consumption of an excessive dose of vitamin D [1]	Practically impossible	Unlikely	**Possible**	**Probable**	Certain
C Severity of the impairment to health following regular consumption of an excessive dose of vitamin D [2]	No impairment	**Mild impairment [reversible]**	**Moderate impairment [reversible]**	Severe impairment [reversible/irreversible]
D Validity of available data	High: The most important data are available and are internally consistent	**Medium: Some important data are missing or inconsistent**	Low: A large volume of important data is missing or inconsistent
E Controllability by the consumer	Controls not needed	**Controllable with precautionary measures**	**Controllable by avoidance**	Not controllable

Fields with a dark blue background indicate the properties of the risk assessed in this opinion
(for more details, see the text of Opinion no. 035/2020 from the BfR dated 31 July 2020).

Explanations

The risk profile is intended to visualise the risk outlined in the BfR Opinion. The profile is not intended to be used to compare risks. The risk profile should only be read in conjunction with the corresponding Opinion.

Row B – Probability of the impairment to health:
[1] – The probability of the impairment may vary. This probability also depends on whether these kinds of high-dose preparations are taken occasionally—and so the recommended UL figure from EFSA of 100 µg is exceeded only occasionally—or whether consumption is frequent (e.g. daily) and this UL figure is therefore exceeded on a regular basis.

Row C – Severity of the impairment to health:
[2] – The severity of the impairment may vary. The same explanation applies here as for row B.

GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT (BfR)

1   Subject of the assessment

In the context of regulatory food monitoring in Germany, the BfR was asked to assess two products placed on the market as food supplements with a vitamin D concentration of 4,000 and 2,000 international units (IU) per tablet, respectively. These products were being sold in tablet form, and contained 100 micrograms (µg) and 50 µg of vitamin D per tablet, respectively, in the form of cholecalciferol. For both products, the recommended consumption was as follows: *"Take 1 tablet every day with a meal and plenty of liquid."* For the product with 100 µg vitamin D, the recommendation *"For adults and children aged eleven and above"* was also made.

2   Results

The use of preparations containing daily doses of 100 µg cholecalciferol or 50 µg cholecalciferol in order to supplement the daily diet with vitamin D is not justifiable from the perspective of nutritional science: even without exposing skin to sunlight, the consumption of 20 µg vitamin D every day is sufficient to cover physiological needs for maintaining bone health for

97.5% of the population. While consuming higher quantities of vitamin D such as 50 or 100 µg cholecalciferol is not associated per se with pathologically elevated calcium excretion in urine (hypercalciuria) and pathologically elevated calcium concentrations in serum (hypercalcaemia)—as an indication of acute vitamin D intoxication—the following facts must be considered concerning the safe use of corresponding products.

1. A product containing 100 µg contains the quantity of cholecalciferol that both the European Food Safety Authority (EFSA) and the US *Food and Nutrition Board* of the *Institute of Medicine* (FNB/IOM) have derived as the *tolerable upper intake level* (UL) for adults and children aged eleven (EFSA) or nine (FNB) and above. This UL is not a figure for recommended consumption but corresponds to the chronic intake quantity for a nutrient from <u>all sources</u> that does not lead to impairments to health in humans according to the respective state of scientific knowledge. Occasional consumption of the nutrient at the level of the UL is not associated with any immediate risk to health. However, the risk for undesirable effects on health rises for increasing intake quantities above the UL. The daily consumption of products containing 100 µg vitamin D or 50 µg vitamin D accounts for 100% and 50% of the UL, respectively (100% for the latter in the case of children under eleven), simply from these individual products. Long-term (i.e. chronic) use of the products by consumers according to the recommended consumption stated by the manufacturer would certainly (in the case of 100 µg) or potentially (in the case of 50 µg) lead to a long-term intake of vitamin D at a level above the UL.

2. Both EFSA and the FNB have derived the UL by using the clinical endpoint of hypercalcaemia, which—with large differences seen between individuals—can be observed at 25-OH-D_3 serum concentrations of 160 nM and above. In a series of large cohort studies, however, a U- or *reverse*-J-shaped relationship was observed between the vitamin D status and overall mortality as well as cardiovascular mortality. According to this relationship, 25-OH-D_3 serum concentrations both below 30–40 nM and above 75 nM correlated positively with overall/cardiovascular mortality. Intervention studies have shown that plasma concentrations of 75 nM can be achieved by intake quantities of 75–100 µg cholecalciferol over a period of six months. While a cause-effect relationship cannot be derived from the epidemiological correlation between the vitamin D status and mortality, this relationship nonetheless indicates that the long-term intake of cholecalciferol in quantities far greater than required to meet the physiological requirements for maintaining bone health is potentially associated with an elevated risk of mortality. This finding is also in line with results from clinical studies. In addition, an elevated risk of pancreatic cancer has also been observed with the increased alimentary intake of vitamin D.

3. In the USA, a significant increase in individuals with 25-OH-D_3 serum concentrations above 50 nM, and also in cases with concentrations above 80 nM, was identified between 2002 and 2011, which, among other factors, was attributed to the general availability of high-dose vitamin D preparations. While the data do not reveal a rise in cases of hypercalcaemia as an indication of acute vitamin D toxicity, the authors nonetheless considered the elevated overall/cardiovascular mortality found at 25-OH-D_3 serum concentrations between 75 and 150 nM, and recommended medical monitoring of serum values in individuals consuming over 4000 IU (100 µg) vitamin D over longer periods of time.

4. In pharmacovigilance data from the German Federal Institute for Drugs and Medical Devices (BfArM), numerous adverse effects are listed for the consumption of cholecalciferol from 25 µg per day (from 12.5 µg per day for children aged 4 and under), most of a gastrointestinal nature. While these data do not permit conclusions to be drawn about cause-effect relationships, a systematic review of the effectiveness of vitamin D and analogue compounds intended to prevent bone fractures in older women and men did reveal a small but significant rise in gastrointestinal symptoms as well as kidney disorders.

In summary, the BfR has not been able to identify any direct health risks that would arise from the occasional consumption of the products in question. In the long term, however, there is moderate but increasing scientific evidence for an elevated risk of mortality with 25-OH-D$_3$ serum concentrations from 75 nM upwards, which can be achieved by the daily consumption of 75–100 µg vitamin D over a period of six months. In the context of an expanding market for foodstuffs enriched with vitamin D, high-dose vitamin D preparations therefore have the potential to result in total intake quantities of vitamin D that are not safe for health.

3 Rationale

3.1 Risk assessment

3.1.1 Characterisation of the substance

'Vitamin D' is an umbrella term for a number of biologically active calciferols. A distinction is made between ergocalciferol (vitamin D$_2$), which occurs in plants and certain fungi, and cholecalciferol (vitamin D$_3$), which occurs in foods of animal origin. Nor is vitamin D a 'vitamin' in the proper sense of the word, since alimentary intake is only essential if endogenous synthesis in the skin in the presence of direct sunlight is inadequate.

The primary function of vitamin D is to act as a regulator of calcium homeostasis, which is essential for bone health. In this process, the formation of the active metabolite calcitriol (1,25-dihydroxycholecalciferol (1,25(OH)$_2$D$_3$)) in the kidneys from 25-hydroxycholecalciferol (25-OH-D$_3$) is stimulated as the level of calcium in the blood falls. This stimulation is not direct: parathyroid hormone is first secreted from the parathyroid glands, which in turn stimulates the kidneys to produce 1,25(OH)$_2$D$_3$. The active vitamin D metabolite raises the level of serum calcium by increasing the absorption of calcium in the gut, reducing calcium excretion via the kidneys and mobilising calcium from the bones (1).

On account of its local, on-demand formation and its short biological half-life of four hours in serum, the active metabolite 1,25(OH)$_2$D$_3$ is not an accurate indicator of vitamin D supply to the body. Accordingly, the serum concentration of the metabolite 25-OH-D$_3$ is used as a marker for vitamin D status: with a biological half-life of 2–3 weeks, it is present in serum at concentrations many thousands of times higher.

3.1.2 Hazard characterisation

Vitamin D presents a hazard to health both if intake is too low and intake is too high. The assessment made in this Opinion focuses on the toxic potential of vitamin D.

A vitamin D overdose is not possible as a result of the body's endogenous production: excessive irradiation by UVB light works to turn pro-vitamin D$_3$ and vitamin D$_3$ into inactive photo-degradation products (1). However, high quantities taken orally can cause an intoxication,

leading to a rise in the concentration of 25-OH-D_3 in serum, while the serum level of the active metabolite 1,25(OH)$_2$$D_3$ remains unchanged (2) or may even fall (3). A vitamin D intoxication manifests itself by elevated calcium levels in serum (hypercalcaemia), although clinical systems may occur after only a short period of time (days to weeks), depending on the quantity consumed.

These clinical signs associated with hypercalcaemia in humans include tiredness, muscular weakness, loss of appetite, nausea, vomiting, constipation, tachycardia, arrhythmias, vascular and soft tissue calcification, weight loss and hypercalciuria. If persistent, hypercalcaemia can lead to kidney stones, kidney calcification and, ultimately, to a loss of renal function (2).

Vitamin D intake quantities associated with a state of intoxication vary from one population group to another, while also showing strong inter-individual variance (3). In its derivation of *dietary reference intakes*, the FNB lists numerous intervention studies in which quantities of vitamin D between 20 and 7,500 µg per day were administered over periods ranging from a few months to years. Hypercalcaemia was regularly observed in studies in which doses of 1,250 µg (50,000 IU) and above were administered, while no cases of hypercalcaemia were identified in studies using doses under 250 µg (10,000 IU). From this, the FNB concluded that a regular intake of vitamin D of 250 µg and above per day increases the risk of developing hypercalcaemia (3). EFSA's Panel on Nutrition also views 250 µg of cholecalciferol per day as the no adverse effect level (NOAEL) (2).

From one individual to another, hypercalcaemia occurs over a very wide range of serum concentrations of 25-OH-D_3 (339–804 nM) (2, 4). In the study by Heaney et al. (2003), the administration of 275 µg vitamin D over 20 weeks to 15 healthy males led to serum levels for 25-OH-D_3 of 220 nM without the occurrence of hypercalcaemia (5). Perez-Barrios et al. (2016) examined 25,567 serum samples from patients from a variety of healthcare facilities and identified a proportion of 1.9% (475 sera) with serum values for 25-OH-D_3 above 160 nM, of which 11.1% (51 sera) also exhibited hypercalcaemia. In most of the sera exhibiting hypercalcaemia, the 25-OH-D_3 concentration was between 161 and 375 nM. In 15 of these individuals, the hypercalcaemia was attributable to vitamin D (6). These figures underline the fact that hypercalcaemic effects from vitamin D doses of around 250 µg/day can be detected and characterised only in intervention studies with a sufficiently high number of participants and a sufficiently long duration. Studies of this kind are not available.

The endpoint of hypercalcaemia essentially characterises the acute toxicity of vitamin D. While acute toxicity does supply important data for deriving a UL, the long-term undesirable effects on health must also be considered. In Evidence Report 158 (*Effectiveness and Safety of Vitamin D in Relation to Bone Health,* 2007), published by the *Agency for Healthcare Research and Quality* (AHRQ) at the *U.S. Department of Health and Human Services*, the authors already warned at the time that indications of the emergence of new risks—such as an elevated risk for pancreatic cancer and increased overall mortality—had been identified for intake quantities of vitamin D above the existing recommended daily intake values (7). The FNB therefore evaluated other studies in which the vitamin D status had been examined in the context of various endpoints. This process identified four cohort studies in which overall mortality had been set as an endpoint (3). All of these studies showed an increased overall mortality for serum concentrations of 25-OH-D3 below 30 nM. This was as expected. However, three of the four studies also demonstrated increased mortality as serum concentrations rose. Overall, these studies revealed a U- or *reverse*-J-shaped correlation between the vitamin D status and overall mortality. One of these three studies was conducted within the framework of the *NHANES III (Third National Health and Nutrition Examination Survey;* 1988–1994, 13,331 test subjects ≥20 years, representative of the US population) for mortality

data from the years 1991–2000 (8) and repeated six years later. In this second follow-up, conducted 15 years after the main study, the *reverse*-J-shaped correlation between the vitamin D status and overall mortality was confirmed as having grown more pronounced (9). The Copenhagen vitamin D study (CopD Study), which examined data from 247,574 individuals, also found a *reverse*-J-shaped correlation between the vitamin D status and overall mortality (10), as well as cardiovascular mortality (11). This study also established a mortality minimum at between 40 and 80 nM 25-OH-D3 in serum.

While many types of epidemiological studies, of which cohort studies are a subtype, cannot be used to substantiate a cause-effect relationship, the comparability of these results from multiple, large-scale population studies does suggest that the effect is real and that suitable studies should be used to verify whether moderately high intake quantities of vitamin D affect cardiovascular parameters.

A number of high-quality intervention studies already available on this topic were analysed by Challoumas et al. (2015), with the following findings: an intervention with vitamin D did not result in positive or negative effects on blood pressure and on cardiovascular events (heart attack, stroke or death), and tended to have negative effects on blood lipids; at the same time, effects on glucose metabolism were not consistent (12). Bjelakovic et al. (2014) prepared a systematic review of 56 studies in which the endpoint of overall mortality had been investigated for a vitamin D intervention. The authors concluded that this intervention with vitamin D_3 seemed to lower mortality for older individuals—whether living independently or in residential homes. In the stratified analyses, however, the result was significant only if individuals with an inadequate vitamin D status had been supplemented with doses of up to 800 IU (20 μg) (13). Another systematic review of the literature conducted by Reid et al. (2016) revealed a correlation between the concentration of calcium in serum and cardiovascular disorders even at normal serum calcium levels. The authors show that the risk of coronary heart disease (CHD) rises by 8% and the risk of death rises by 13% for each standard deviation of elevated serum calcium (14). Rubin et al. (2007) investigated whether subclinical parameters for cardiovascular health become altered even at high-normal levels of serum calcium. The authors measured the thickness of existing plaques in the carotid artery (*aorta carotis*), which is considered predictive for the development of cardiovascular disorders, in 1,194 healthy test subjects. The authors found that all individuals who exhibited any plaques at all had calcium concentrations in the high-normal range, while concentrations for individuals without plaques were in the low-normal range. Calcium concentrations in serum also correlated positively with plaque thickness (15). In a population of 4,194 non-smokers, Kamycheva et al. (2013) also investigated relationships between the thickness of the intima media (IMT) and the total area of plaques in the carotid artery with serum calcium and the vitamin D status. The authors found that males with higher serum values for 25-OH-D_3 had a significantly higher risk of an IMT thickness in the upper quartile, while females with higher 25-OH-D_3 values exhibited a significantly higher risk of larger plaque areas (16). In a population study involving 1,293 test subjects, Rathod et al. (2015) demonstrated a positive correlation between the vitamin D status and calcium excretion (17).

These clinical studies could be interpreted as offering indications of a causative *reverse*-J-shaped correlation between the vitamin D status and cardiovascular mortality. The question of whether the vitamin D status (independently of the active metabolite calcitriol) influences serum calcium concentrations in the normal range—and under what conditions—therefore requires urgent clarification.

From a review of case-control studies conducted by the international Pancreatic Cancer Case-Control Consortium (PanC4), the increased intake of vitamin D is also suspected to be

a risk factor for pancreatic cancer (18). This suspicion cannot be verified on the basis of the current available knowledge, however.

If the adverse drug reactions database maintained by the BfArM is searched using the term 'cholecalciferol', further specified by 'used as a standalone preparation', 26 suspected cases can be found in which vitamin D preparations were taken as a standalone medicinal product. Where specified, the preparation consumed typically contained 1,000 IU (25 µg) vitamin D for adults and 500 IU (12.5 µg) vitamin D for children aged 4 and under. An evaluation of the effects by organ system showed that gastrointestinal adverse effects were the effects most commonly reported (23%). From pharmacovigilance data, however, no cause-effect relationship can be identified—only suspected cases. However, a systematic review of the effectiveness of vitamin D and analogue compounds taken with the aim of preventing bone fractures in older women and men did reveal a small but significant rise in both gastrointestinal symptoms as well as kidney disorders (19).

3.1.3 Exposure

In humans, exposure to vitamin D results from the duration of exposure of the skin to UVB radiation (in sunlight or at a solarium) as well as the consumption of food or medicinal products containing vitamin D. This exposure is evaluated by analysing serum levels of 25-OH-D_3. A serum concentration of 50 nM 25-OH-D_3 is considered to be the reference value for adequate vitamin D supply in 97.5% of the population. Serum values of 30 nM and below indicate an elevated risk of a vitamin D deficiency, while serum values of 125 nM and above present an elevated risk of toxic effects, according to the *Institute of Medicine* (IOM) (3).

In Germany, representative, nationwide data on vitamin D supply in the general population were last obtained by the Robert Koch Institute (RKI) from its 'Study on the Health of Children and Adolescents in Germany' (KiGGS), conducted from 2003 to 2006 (20), and its 'Study on Adult Health in Germany' (DEGS), which was conducted from 2008 to 2011 (21). Both studies utilised an immunological method for measurements, although this method is no longer reflective of the current state of vitamin D analysis. As part of an international vitamin D standardisation programme conducted by the US *National Institutes of Health* (NIH), reserve samples from 14 large-scale European studies (including both DEGS and KiGGS) were therefore measured using a liquid chromatography method coupled with mass spectroscopy. From these results, correction factors for all studies were then determined, which were then applied to correct the original findings. The corrected values obtained for DEGS and KiGGS are applied to assess exposure in this Opinion (22).

In children, the corrected serum concentrations for 25-OH-D_3 yield a median of 52.9 nM (SD 19.2 nM), with the 95th percentile at 82.9 nM. Serum levels below 25 and 30 nM are found in 6% and 11.9% of children, respectively, while 55.5% and 16.2% have serum levels above 50 and 75 nM, respectively.
In adults, the corrected serum concentrations for 25-OH-D_3 yield a median of 47.7 nM (SD = 18.1), with the 95th percentile at 84 nM. Serum levels below 25 and 30 nM are found in 4.2% and 12.9% of adults, respectively, while 45.5% and 9.1% have serum levels above 50 and 75 nM, respectively.

As a result, the serum values for 25-OH-D_3 for both children and adults in Germany essentially reflect a population with an adequate supply of vitamin D, with a small proportion of individuals exhibiting a risk of insuffiency. From the corrected data for overall distribution, it is also clear that only very few individuals are likely to exhibit serum 25-OH-D_3 levels in excess

of 125 nM. Nonetheless, 16.2% of children and 9.1% of adults already have serum levels in ranges for which an increased risk of mortality has been observed in studies.

The serum values determined by KiGGS and DEGS correspond to a situation where around 80–90% of vitamin D is being provided as a result of solar irradiation, while only 10–20% is being obtained via the diet. According to figures from the National Food Consumption Study (NVS) II, 2–4 µg vitamin D are consumed daily by adolescents and adults in food (primarily fish, spreadable fats, eggs and dairy produce) (23). Until recently, only very few foodstuffs fortified with vitamin D were commercially available within Germany. Even food supplements typically contain only 5 µg vitamin D per recommended daily dose—and this is especially true in the case of multivitamins. This roughly equates to the quantity with which endogenous synthesis would need to be supplemented by oral intake (25% of the reference value). In recent years, however, an increasing number of single-nutrient supplements containing 20 or 25 µg vitamin D per recommended daily dose have been launched on the market.

The situation is also being drastically altered by a major trend towards fortification of foods with vitamin D. In the EU, the enrichment of foodstuffs with vitamin D may be regulated by the Fortification Regulation (Regulation (EC) No 1925/2006) (24) or the Novel Food Regulation (Reg. 258/97/EC) (25). In accordance with the Fortification Regulation, vitamin D may be added to foods in the form of ergocalciferol or cholecalciferol. As with other vitamins and minerals, however, no legal maximum safe levels have been defined in the context of enrichment with vitamin D (26). With only a few exceptions, the enrichment of food with vitamin D in Germany requires a specific permit, which must be obtained from the German Federal Office of Consumer Protection and Food Safety (BVL). At the time of writing, the market for vitamin D-enriched products includes margarines and mixed fats, cooking oils, vegetable creams, cream cheeses and breakfast cereals.

The Novel Food Regulation defines foods and food ingredients as 'novel' if these were not yet consumed to a significant degree by populations in the European Union before 15 May 1997 (effective date for the Regulation). This definition also includes foods with non-conventional methods of production. Foods whose vitamin D concentration has been raised by UV irradiation are therefore also 'novel'. At the present time, for example, a UV-irradiated yeast for use in baking and food supplements has been approved as a novel food, as has a wider range of products that includes UV-irradiated milk, bread and mushrooms.

3.1.4   Risk characterisation

From the vitamin D statuses obtained for children and adults, it can be seen that vitamin D intoxication from the consumption of food has so far been unlikely in Germany. Some 16% of children and adolescents and around 9% of adults are nonetheless exposed to a potentially increased risk of mortality from vitamin D, however. Whether the high plasma levels were present over the long term in specific individuals in both studies or reflected only a 'snapshot' of levels at the time of the survey is unclear. In the latter case, the actual risk of increased mortality would be considered to be low.

However, one may assume that changing practices in the fortification of foods with vitamin D together with an increase in the daily dose of vitamin D consumed from preparations marketed as food supplements will, in the near future, lead to a rise in the proportion of individuals who are potentially exposed to an increased risk of mortality as a result of a chronically elevated intake of vitamin D.

Dudenkov et al. (2015) retrospectively examined the increase in individuals with 25-OH-D$_3$ levels above 50 nM in a single region of the US (Olmsted County, Minnesota) for the period 2002 to 2011 (27). To do so, the authors used data from 20,308 individuals from various healthcare centres. The authors identified a rise in values over 50 nM from 9 to 233 cases per 100,000 person-years, reflecting an approximately 26-fold increase. The incidence of serum concentrations above 80 nM also increased significantly. However, the increase in cases of serum concentrations of 25-OH-D$_3$ over 100 nM was slight, and the incidence trend was not significant. Among individuals with serum 25-OH-D$_3$ levels above 50 nM with simultaneous hypercalcaemia, reasons other than vitamin D (e.g. elevated parathyroid hormone) could be excluded in four cases. One case exhibited signs of acute vitamin D intoxication (at a serum level of 906 nM for 25-OH-D$_3$). Within the overall population, however, no correlation was found between the vitamin D status, serum calcium concentrations and the occurrence of hypercalcaemia. The primary reason for the rise was identified by the authors as the consumption of high-dose vitamin D preparations, which have been far more extensively promoted by public information campaigns and physicians in the USA over the last few years.

While this study did not identify any signs of an increase in acute vitamin D toxicity, the authors do cite the risk of an increase in overall/cardiovascular mortality, and also recommend that vitamin D is taken at a daily dose of 4000 IU (100 µg) or higher only under medical supervision, with regular testing of serum 25-OH-D$_3$ and calcium (27) levels.

The overall insight to be obtained from this study is the certainty—rather than the mere probability—that the availability of high-dose vitamin D preparations has a very real potential to raise the serum levels of 25-OH-D$_3$ in a population to a significant degree. In addition, the regular consumption of high-dose preparations works to create a situation where specific individuals actually exhibit a vitamin D status in ranges correlated with an elevated risk of mortality on a continual rather than merely occasional basis.

3.2 Other aspects

In recent years, new reference values for the intake of vitamin D have been specified in the USA (by the FNB), in Europe (by the EFSA Panel on Nutrition, Novel Foods and Food Allergens) and in Germany (by the DGE) (3, 28, 29). The FNB and EFSA each recommend 15 µg vitamin D daily (for most age groups except infants) as an adequate intake quantity to maintain bone health, while the DGE has set its estimate for this figure to 20 µg/day. Since endogenous synthesis is more or less reduced in winter in various latitudes and since UV irradiation should not be artificially induced due to a risk of skin cancer, recommendations have been derived that largely (FNB and EFSA) or completely (DGE) discount the endogenous synthesis of vitamin D. In its derivation, the FNB integrated the literature data on the rise of serum 25-OH-D$_3$ by the oral administration of vitamin D into a model that produces a figure of 600 IU (15 µg) as being adequate for all age groups in northerly latitudes in order to generate desirable concentrations in plasma of around 50 nM (3). In a comparable procedure, EFSA also derived a daily dose of 15 µg vitamin D as an adequate intake quantity for the population from the first year of life onwards (28). The DGE based its calculations on a study by Cashman et al. (2008): conducted in Ireland over the winter months, this study used a vitamin D intake (as a supplement) of 10 µg per day to achieve a 25(OH)D$_3$ concentration in serum of over 50 nM in about 50% of the population, with a daily intake of around 20 µg achieving this in 90–95% of the population (29, 30). A study by Heany et al. (2003) also showed that an additional daily intake of approx. 12 µg vitamin D was able to prevent serum concentrations of 25-OH-D$_3$ from declining over winter (5).

Based on the available data, a daily intake of more than 20 µg vitamin D via foodstuffs—a category that also includes food supplements—can therefore not be justified from the perspective of nutritional science. This position is also held by the BVL/BfArM Joint Commission of Experts on the Classification of Substances (31).

Further information on food supplements is available from the BfR website

A–Z Index of Food Supplements:
https://www.bfr.bund.de/en/a-z_index/food_supplements-129789.html

Selected Questions and Answers on vitamin D:
https://www.bfr.bund.de/cm/349/selected-questions-and-answers-on-vitamin-d.pdf

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