Vitamin D

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
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 D is a fat-soluble vitamin and prohormone that, once converted to its active form, calcitriol (1,25(OH)2D), is essential for calcium and phosphate homeostasis, which preserve neuromuscular and cellular function (Holick 1996; IOM 2011). Vitamin D maintains bone and modulates processes, such as immune function and the cell cycle (Aranow 2011; IOM 2011). The major forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is primarily manufactured and added to foods, while vitamin D3 is synthesized in human and animal skin and is consumed via animal-based diets (IOM 2011; EFSA 2023).

Published by Council for Responsible Nutrition (CRN), Washington, D.C.

Vitamin D2 is synthesized from the provitamin ergosterol, which is found in plants, fungi, and yeast that are exposed to UV-B irradiation (Dominguez et al. 2021; EFSA 2023). Vitamin D3 is created from the provitamin 7-dehydrocholesterol in humans and animals after UV-B irradiation in the skin and is also produced in some plants (e.g., lichens) (Dominguez et al. 2021; EFSA 2023). The only structural differences between vitamin D2 and vitamin D3 are the side chains (IOM 2011). The vitamin D2 and D3 forms are currently treated as bioequivalent; however, studies indicate that the half-life of 25(OH)D2 may be 10% shorter than that of 25(OH)D3 due to the vitamin D binding protein's slightly lower affinity for metabolites of vitamin D2 than those of D3 (Jones et al. 2014). Further, several studies indicate that vitamin D3 is more potent in raising and maintaining serum 25(OH)D concentrations and produces 2- to 3-fold greater storage of vitamin D than equimolar vitamin D2 (Armas et al. 2004; Durrant et al. 2022; Oliveri et al. 2015; Trang et al. 1998; Tripkovic et al. 2017). Meta analyses also indicate that, compared to ergocalciferol, cholecalciferol intervention is more efficacious in improving vitamin D status (e.g., serum levels of total 25(OH)D and 25(OH)D3) and regulating parathyroid hormone (PTH) levels, when controlling for participant demographics, dosage and vehicle of supplementation (Balachandar et al. 2021; Brown et al. 2025; Tripkovic et al. 2012). While this suggests variance in bioavailability between vitamin D2 and D3, heterogeneity between the available studies makes it difficult to establish a relative conversion factor. Further research is needed to establish whether vitamin D2 and D3 elicit different changes in overall vitamin D metabolism, which might inform clinical recommendations for vitamin D3 supplements versus D2 (Balachandar et al. 2021; Brown et al. 2025; Tripkovic et al. 2012).

Vitamin D is required in quantities smaller than any other fat-soluble vitamin. In humans, the primary source of vitamin D is endogenous synthesis in the skin following exposure to sunlight (Dominguez et al. 2021). The largest contribution to dietary intake of vitamin D is vitamin D3 in fish liver oils, eggs, milk, liver, and fortified foods (Delage 2017; EFSA 2023). Dietary supplements contain either vitamin D2 or vitamin D3 at a dose range of 400 to 50,000 IU (Delage 2017; EFSA 2023; NIH 2025). The conversion of international units to metric weights for vitamin D2 and D3 is the same: 1 µg equals 40 IU; 0.025 µg equals 1 IU.

Of note, a synthetic compound, calcidiol monohydrate (25-hydroxyvitamin D3 monohydrate), was recently evaluated as a Novel Food by the EFSA (2021) and included in the EFSA (2023)

determination of an UL for vitamin D based on a vitamin D equivalency factor. Calcidiol monohydrate was included in the literature search for this chapter update; however, no studies were identified that met the inclusion criteria. Therefore, calcidiol monohydrate is not included in this vitamin D chapter, which focuses on the derivation of UL values for supplemental vitamin D (as vitamin D2 and vitamin D3) in adults.

Bioavailability

The bioavailability of vitamin D2 and vitamin D3 ranges from 55-99% from both food and food supplements (EFSA 2023; Borel et al. 2015). Vitamin D2 and vitamin D3 are absorbed in the distal small intestine through utilization of available bile acids and formation of micelles. The absorbed vitamin D2 and vitamin D3 are incorporated into chylomicrons, which enter systemic circulation via the lymphatic system. Vitamin D from the diet is released from chylomicrons at the liver to undergo hydroxylation (Borel et al. 2015; EFSA 2023). Vitamin D produced from sun exposure and calcidiol is transported in plasma bound to vitamin D-binding proteins (Dominguez et al. 2021). These hydroxylated forms of vitamin D are released from vitamin D-binding proteins at various tissues including bone, intestine, kidney, pancreas, brain, and skin. Vitamin D is present in adipose tissue and is stored long-term in muscle and liver tissues (Dominguez et al. 2021; EFSA 2023).

Vitamin D from endogenous production, foods, or supplements is inert and must undergo two hydroxylation reactions in the body for activation. The first hydroxylation reaction occurs in the liver, generating 25-hydroxy vitamin D (25[OH]D, as D2 or D3) and then the kidney converts 25(OH)D (as D2 or D3) to the active hormones, 1,25-dihydroxy vitamin D (as D2 or D3) and 24,25-dihydroxy vitamin D (as D2 or D3) (Bikle 2025). The plasma half-life of 1,25-dihydroxy vitamin D (D2 or D3) is approximately 4-8 hours, while the plasma half-life of 25(OH)D is approximately 13-15 days (Dominguez et al. 2021; EFSA 2023; NIH 2025). Vitamin D degradation products are excreted in bile and in the feces (EFSA 2023).

Safety Considerations

Excess exposure to sunlight does not lead to vitamin D toxicity as vitamin D synthesis in the skin is slowed once dietary vitamin D intakes are sufficient and blood levels of the activated

forms are high (Holick 1999; Hathcock et al. 2007). Dietary vitamin D can, however, produce toxic effects when consumed in very large quantities, especially over an extended period of time. As discussed below, potential adverse effects are mediated by hypercalcemia resulting from excess vitamin D and can include permanent mineral deposits in soft tissues, renal failure, cardiac arrhythmias, and even death (Delage 2017; NIH 2025). The amount of daily vitamin D ingestion needed to produce adverse effects has been reported to vary widely. For example, older clinical data have suggested that, in most adults, daily intake above 50,000 IU (1.25 mg vitamin D) is needed to produce toxicity (Miller and Hayes 1982; Holick et al. 2015). More recent reviews conclude levels at or below 10,000 IU (250 µg vitamin D per day) are very unlikely to be associated with vitamin D toxicity, also known as "hypervitaminosis D" (Tebben et al. 2016; Delage 2017).

Treatment with vitamin D or 25(OH)D does not generally increase the serum concentrations of active metabolites (calcitriol, 1-alpha,25-dihydroxycholecalciferol, or 1,25-dihydroxy vitamin D) (Barger-Lux et al. 1998; Tebben et al. 2016). However, prolonged intake of excess vitamin D may lead to predictable increases in plasma 25(OH)D concentrations (IOM 2011; NIH 20; EFSA 2023), and the increase is directly proportional to the vitamin D dose (Barger-Lux et al. 1998). It is difficult to determine the exact serum vitamin D concentrations associated with vitamin D toxicity; however, in general, serum 25(OH)D concentrations over 200 nmol per L to 250 mmol per L (80 ng per mL) are thought to cause symptoms of hypercalcemia (discussed below), but this is dependent on several factors, especially calcium intake (Dudenkov et al. 2015; Tebben et al. 2016; Das et al. 2023; EFSA 2023).[1]

Nonetheless, excess vitamin D can cause increased calcium absorption in the gastrointestinal tract, initially causing an increase in urine calcium (i.e., hypercalciuria) as the kidneys compensate by excreting more calcium. In addition, as circulating levels of 25(OH)D increase, PTH levels are suppressed, leading to decreased tubular reabsorption of calcium and contributing to increased urinary concentrations. Once the system regulation becomes overwhelmed, serum calcium levels can increase above the normal upper limit of 10.2 mg per dL; clinical

[1] EFSA (2023) stated that serum total 25(OH)D concentrations ≥ 200–220 nmol per L are necessary to result in vitamin D toxicity.

hypercalcemia is typically defined as serum calcium > 11.1 mg per dL (Tebben et al. 2016; Delage 2017; NIH 2025; EFSA 2023). Diagnosis of hypercalcemia mediated by vitamin D excess is typically based on the occurrence of elevated serum calcium and certain vitamin D metabolite concentrations together with reduced PTH levels (Holick et al. 2015; Tebben et al. 2016). When PTH is suppressed, hyperphosphatemia is also observed due to decreased clearance of phosphate. Hypercalcemia can lead to a wide range of signs and symptoms, from dehydration to permanent mineral deposits in soft tissues, including muscle, heart, kidney, and cartilage, if left untreated for a long period of time (Delage 2017). Continued intake of toxic levels can have severe and persistent adverse consequences, such as renal failure, cardiac arrhythmias, and even death (NIH 2025).

Although the IOM (2011) considered hypercalcemia to be the critical effect in vitamin D toxicity based on reports of anecdotal cases of accidental overdose, no clinical trials reviewed as part of this update have used levels sufficiently high to produce such high blood levels of calcium. As discussed below, persistent hypercalcemia in subjects taking 250 µg (10,000 IU) per day in long-term clinical trials has not been reported (Vieth et al. 2001; Heaney et al. 2003; Hollis and Wagner 2004; Mastaglia et al. 2006; Wagner et al. 2006; Jorde et al. 2008; Hollis et al. 2011; Burnett-Bowie et al. 2012; Grimnes et al. 2012; Ponda et al. 2012; Diamond et al. 2013; Drincic et al. 2013; Gallagher et al. 2013; Wamberg et al. 2013; Rorie et al. 2014; Hin et al. 2016; Schwartz et al. 2016; Wagner et al. 2016; Aloia et al. 2018; Enkhmaa et al. 2019; Billington et al. 2020; Shirvani et al. 2020; Johnson et al. 2022; Ramot et al. 2022; Das et al. 2023; Guella et al. 2023; Mangas-Sánchez et al. 2023; Takacs et al. 2023; Bowman et al. 2024; Porto et al. 2025; Shah et al. 2025; Thouvenot et al. 2025). In addition, no cases of hypercalcemia were identified at doses up to 357 µg per day for 1 year (Rafii et al. 2019) or up to 2,000 µg per day for 3 consecutive months (6 months total) (Ganie et al. 2023). Instead, evidence supporting the potential relationship between vitamin D and hypercalcemia comes from reports of anecdotal cases of accidental overdose (IOM 2011; NIH 2025). Of important note, in certain disease conditions such as primary hyperparathyroidism, sarcoidosis, mycobacterium infections such as tuberculosis, lymphoma, or idiopathic hypercalcemia, toxicity can occur at levels of vitamin D intake lower than those in the general population (EVM 2003; Delage 2017). As such, patients with these conditions are excluded from CRN's supplemental UL for the general population.

In 2023, the EFSA assessed the available human clinical data reporting persistent hypercalcemia and/or hypercalciuria associated with excess vitamin D intake. In its evaluation, the EFSA included studies that administered doses of at least 100 µg vitamin D per day and were long enough in duration to detect such an effect(s) (i.e., at least six weeks) (EFSA 2023). The EFSA defined persistent hypercalcemia and/or hypercalciuria and only included studies that measured serum and/or urine calcium levels in all participants at least two times after baseline. Of note, the EFSA (2023) relied on study authors' criteria for identification and conclusions of hypercalcemia and/or hypercalciuria. For example, the EFSA Panel considered multiple methods of measurement for hypercalciuria (e.g., 24-hour urine calcium, spot urine calcium, and urine calcium to creatinine ratios). Following its review, the EFSA (2023) concluded that vitamin D supplementation alone up to 250 µg per day for 5-6 months does not increase the risk of developing persistent hypercalcemia (Drincic et al. 2013; Shirvani et al. 2020). However, based on two RCTs in which 250 µg vitamin D per day was administered with concomitant supplemental calcium (Aloia et al. 2018; Billington et al. 2020), the EFSA concluded that vitamin D supplementation at a dose "of 250 µg per day for a period of 1–3 years (in co-supplementation with calcium to reach adequate intakes for the study population) increases the risk of persistent hypercalciuria by approximately 3 times as compared to doses of vitamin D in the range of adequate intakes (10–15 µg/day), even when calcium supplementation was reduced or withdrawn." As discussed below in the *Official Reviews* section, the EFSA derived an UL of 100 µg per day for vitamin D based on these findings.

Given the vast volume of clinical trials conducted with vitamin D, the literature search for CRN's assessment was focused on clinical studies reporting on the key endpoints of hypercalcemia and hypercalciuria as part of their monitoring for safety following intervention with vitamin D. In addition, given that the EFSA Panel (2023) conducted a comprehensive review of available RCTs and carried forward these same potential markers of vitamin D toxicity as the basis for deriving its UL value, the date of the EFSA's comprehensive literature search used to support its evaluation (i.e., March 2022) was selected as the start date for CRN's screening approach. Thirty studies published after this date were identified that met the inclusion

criteria for the current update.[2] Of these, 22 studies met the additional criteria of administration of at least 100 µg vitamin D per day for a least 6 weeks in adults. A total of 51 studies—29 studies in adults identified by the EFSA (2023, Appendix C2) and 22 studies identified by CRN in its updated search—were reviewed in detail for this update. A full literature review is outside the scope of this chapter; however, an overview of the information reviewed in these 51 studies is summarized below.

Of the 51 studies that met the inclusion criteria, only 42 measured serum and/or urine calcium levels in all participants at least two times after baseline. These 42 studies were further evaluated to assess the occurrence of hypercalcemia and/or hypercalciuria as reported by each study's authors based on serum and/or urine measurements. Where identified, occurrences were defined as 1) persistent, 2) transient, or 3) unclear. While all findings are discussed for each study below, only persistent cases were considered as unequivocal evidence of an adverse effect. Persistent cases were defined as those confirmed by the study authors based on retesting within a given timeframe (with the elevated level persisting) or based on the number of individuals with recurrent elevated calcium levels being reported for at least two time points.

No cases of persistent hypercalcemia were reported in any interventional clinical study identified as part of this update. Relevant data were available from 41 studies, as all but one study (Ceglia et al. 2013) analyzed serum calcium levels in participants. Thirty-two studies were determined by the study authors to have zero cases of hypercalcemia following exposure to vitamin D at highest levels administered, ranging from 100 µg per day to 250 µg per day for 8 weeks to 3 years (Vieth et al. 2001; Heaney et al. 2003; Hollis and Wagner 2004; Mastaglia et al. 2006; Wagner et al. 2006; Jorde et al. 2008; Hollis et al. 2011; Burnett-Bowie et al. 2012; Grimnes et al. 2012; Ponda et al. 2012; Diamond et al. 2013; Drincic et al. 2013; Gallagher et al. 2013; Wamberg et al. 2013; Rorie et al. 2014; Hin et al. 2016; Schwartz et al. 2016; Wagner et al. 2016; Aloia et al. 2018; Enkhmaa et al. 2019; Billington et al. 2020; Shirvani et al. 2020; Johnson et al. 2022; Ramot et al. 2022; Das et al. 2023; Guella et al. 2023; Mangas-Sánchez et al. 2023; Takacs et al. 2023; Bowman et al. 2024; Porto et al. 2025; Shah et al. 2025; Thouvenot et al. 2025). In addition, no cases of hypercalcemia were identified at doses up to 357 µg per day

[2] Literature search conducted January 2026. CRN's established methodology was followed with the additional criteria described herein.

for 1 year (Rafii et al. 2019) or up to 2,000 µg per day for 3 consecutive months (6 months total) (Ganie et al. 2023). Transient cases of hypercalcemia were reported in one study at 120 µg per day; of note, no hypercalciuria cases were identified in this study (Gallagher et al. 2012). Comparatively, only one case of transient hypercalcemia was reported in an older 1-year study with supplemental vitamin D at a dose of 2,500 µg per day, although no criteria for such was provided by study authors (Brohult and Jonson 1973). Cases of hypercalcemia were concluded in CRN's assessment to be unclear in four studies administering 100 to 250 µg per day (Aloia et al. 2013; Roth et al. 2018; Holden et al. 2024; Jódar-Gimeno et al. 2024).

Hypercalciuria based on urine calcium levels in all participants measured at least two times after baseline was analyzed in 19 of the 42 studies identified in this update. The methods of measurement varied across studies and included 24-hour urine, spot urine calcium, urine creatine-corrected calcium, and urine calcium to creatinine ratios. In most studies, urinary calcium measures adjusted for urinary creatinine, which is standard practice in the clinical setting to standardize measurements and account for variability in urine calcium due to factors such as hydration, time of day, and kidney function. However, not all studies adjusted for creatinine, as discussed below. Seven studies were determined by the study authors to have zero cases of hypercalciuria following exposure to vitamin D at the highest levels administered, ranging from 100 µg per day to 214 µg per day for 10 weeks to 2 years (Wagner et al. 2006; Hollis et al. 2011; Gallagher et al. 2012, 2013; Takacs et al. 2023; Porto et al. 2025; Thouvenot et al. 2025). In one RCT conducted in healthy, vitamin D-deficient adults, vitamin D doses of 600, 1,000, or 2,000 µg per day were administered. Administration at 600 or 1,000 µg vitamin D per day was not associated with any (zero) cases of hypercalciuria for 3 consecutive months (6 months total) (Ganie et al. 2023). The same study reported transient hypercalciuria in three out of 153 subjects at 2,000 µg per day (as either 2,000 µg per day or 60,000 µg per month). Cases of transient hypercalciuria were also reported in two studies administering 100 µg per day (Ceglia et al. 2013; Rorie et al. 2014). Lastly, potential cases of hypercalciuria were determined to be unclear based on the study data for seven human trials with daily vitamin D doses ranging from 100 to 357 µg per day (Vieth et al. 2001; Mastaglia et al. 2006; Aloia et al. 2013; Rafii et al. 2019; Ramot et al. 2022; Das et al. 2023; Shah et al. 2025).

Only two of the identified studies reported cases of persistent hypercalciuria, as defined by the criteria established by the study authors. In the first, Billington et al. (2020) reported an increase in risk of persistent hypercalciuria in older adults at vitamin D doses of up to 250 µg per day, co-administered with calcium, for three years. In this study, supplemental vitamin D was administered at doses of 10, 100, or 250 µg per day. In addition, supplemental calcium was administered when needed to achieve a total dietary intake of 1,200 mg calcium per day.[3] Billington et al. (2020) reported that hypercalciuria (based on 24-hour urine calcium; using a cutoff of 300 mg per day or higher)[4] was observed in 4.3% of participants at baseline and that recurrent hypercalciuria was observed in 4.0%, 6.4%, and 11.3% of the treatment groups, respectively. The odds ratios (ORs) for incidence hypercalciuria in the 100 µg per day and 250 µg per day groups compared to the 10 µg per day group were found to be 1.6 and 3.0, respectively. It is important to note, however, that Billington et al. did not correct 24-hour urinary calcium for creatinine. The lack of correction for creatinine is considered a limitation by CRN and brings into question the utility of these measurements and conclusions regarding hypercalciuria from the Billington et al (2020) study. It is noteworthy, however, that the study authors reported the peak mean (standard deviation [SD]) of serum 25(OH)D concentration to be 198 (42) nmol/L in the 250 µg per day group, indicating some individuals were in the range high enough to be associated with potential vitamin D toxicity (i.e., > 200 nmol/L). In addition, the authors also noted that PTH concentrations in participants were significantly lower during hypercalciuria episodes relative to normocalciuria.

The second RCT reported a similar increased risk of persistent hypercalciuria at vitamin D doses of up to 250 µg per day co-supplemented with calcium for one year (Aloia et al. 2018). In this study, supplemental vitamin D was administered at doses of 15 or 250 µg per day in addition to 1,200 mg calcium per day. Calcium supplementation was subsequently reduced to 600 mg per day when recurrent hypercalcemia and/or hypercalciuria were observed and ultimately stopped altogether if either finding persisted. Aloia et al. (2018) reported that hypercalciuria occurring on at least two time points (i.e., persistent hypercalciuria), based on 24-hour urine calcium using a cut-off of 250 mg per day, was observed in 14% (low dose) and 30% (high dose) of the treatment groups, respectively. The crude OR for incidence of hypercalciuria in the 250 µg per

[3] Calcium doses not specified
[4] 7.5 mmol per day for participants < 75 kg body weight; 0.1 mmol per kg per day for those heavier than 75 kg

day group compared to the 15 µg per day group was 2.8. It is important to note, however, that the criteria that Aloia et al. used for defining hypercalciuria (250 mg per day) is at the lower end typically employed in the clinical setting, which generally ranges from 250 to 350 mg per day. While some experts suggest that optimal urinary calcium levels are below 250 mg per day, it is generally thought that 100 to 300 mg per day is the expected level in individuals eating a normal diet.[5] If a cut-off of 300 mg per day were used, the creatinine-corrected 24-urinary calcium levels reported in Aloia et al. (2018) would fall at or below this level, as the mean (SD) was reported to be 261.0 (163.1-300.0). The fact that 19 subjects (29%) in the lower treatment group in this study had at least one episode of hypercalciuria further indicates that the cut-off of 250 mg per day was potentially too conservative in this study. For additional context, other studies included in this review used 300 mg per day as the cut-off (e.g., Billington et al. 2020). Despite this limitation identified by CRN, it is noteworthy that the study authors reported the mean (SD) serum 25(OH)D concentration to be 216 (66) nmol/L in the 250 µg per day group, indicating some individuals were in the range associated with potential vitamin D toxicity (i.e., > 200 nmol/L). Finally, the study authors noted that calcium intake was statistically significant when assessed in the model as a time-varying covariate, suggesting calcium co-supplementation contributed to the higher occurrence of hypercalciuria in the higher vitamin D group when compared to the lower dose group. The authors also noted that subjects with persistent hypercalciuria were no longer taking calcium supplements at the end of the study.

Official Reviews

Expert Group on Vitamins and Minerals (EVM 2003). The UK's EVM did not find the available data sufficiently compelling to identify a NOAEL or a LOAEL. Instead, it set a guidance level of 25 µg vitamin D per day based on studies by Vieth et al. (2001) at 100 µg per day and Johnson et al. (1980) at 50 µg per day. Johnson et al. (1980) observed an increase in serum calcium levels and reported two subjects developed hypercalcemia (defined as serum calcium levels greater than 2.75 mmol/L). Vieth et al. (2001) did not observe any evidence of hypercalcemia and EVM noted that this study had "low statistical power to detect" differences

[5] https://www.ncbi.nlm.nih.gov/books/NBK482482/; https://johnshopkinshealthcare.staywellsolutionsonline.com/library/testsprocedures/LabTests/167,calcium_urine; https://www.uclahealth.org/medical-services/surgery/endocrine-surgery/patient-resources/patient-education/endocrine-surgery-encyclopedia/urine-calcium-test; https://www.ucsfhealth.org/care/medical-tests/calcium-urine

in hypercalciuria between treated and untreated groups. The EVM concluded that long-term use of supplements of 25 µg per day is "well tolerated," but did not establish a safe upper limit.

IOM (2011). The IOM has established an UL of 100 µg (4,000 IU) per day for vitamin D, based on downward extrapolation from the NOAEL of 250 µg (10,000 IU) per day, as derived from multiple clinical trials in a risk assessment using UL methodology (Hathcock et al. 2007). Hypercalcemia was used as the initial indicator for vitamin D toxicity. To take into account uncertainties from emerging data regarding all-cause mortality, chronic disease risk, and falls at serum 25(OH)D levels of approximately 75 to 125 nmol per L, the IOM considered the findings of Heaney et al. (2003) in establishing a UL. In this study, intakes of 5,000 IU vitamin D per day for 160 days resulted in serum 25(OH)D levels that did not exceed 150 nmol per L and serum calcium levels within normal ranges. The UL was set at 20 percent below 5,000 IU (i.e.¸4,000 IU) because of the uncertainties surrounding the data and the reliance on one study. The IOM intended "not to determine that certain levels of intake definitively cause harm, but rather to decide whether the emerging data were sufficiently compelling to warrant caution relative to vitamin D intakes."

EFSA (2012, 2023). The EFSA 2012 Opinion derived an UL of 100 µg vitamin D per day based on a NOAEL of 250 µg per day (after application of a UF of 2.5) that was supported by two studies in which doses of 234 to 275 µg vitamin D3 per day for 8 weeks to approximately 5 months did not result in hypercalcemia in healthy young men (Barger-Lux et al. 1998; Heaney et al. 2003). In 2023, the EFSA updated the Scientific Opinion on the UL for vitamin D and concluded that the critical effect was persistent hypercalcemia and hypercalciuria. The assessment did not consider the Barger-Lux et al. (1998) study to be sufficient for inclusion because only one serum calcium measurement was conducted. As discussed in detail in the *Safety Considerations* section, the Panel did not identify hypercalcemia in available RCTs. However, based on two RCTs with vitamin D and calcium co-supplementation, the EFSA Panel considered 250 µg per day to be a LOAEL based on persistent hypercalciuria (as defined by the authors) and continued using the UF of 2.5 to account for the absence of a NOAEL. The Panel derived an UL of 100 µg VDE per day and concluded that chronic consumption at this level is not expected to pose a risk of adverse health effects. This UL applies to dietary intake of vitamin D from all sources, including fortified foods and food supplements and to all forms of vitamin D

(vitamin D2, vitamin D3, and calcidiol monohydrate) (EFSA 2023).

Other potential adverse health effects that were evaluated for risk by the EFSA (2023) included: kidney stones, cardiovascular disease, cancer, and cause-specific/all-cause mortality. The EFSA Panel concluded that evidence was insufficient for these effects, specifically:

- The available evidence on the relationship between vitamin D intake and risk of adverse musculoskeletal effects (e.g., on bone) cannot be used alone as a critical endpoint on which to base the UL for vitamin D.
- The available evidence on the relationship between vitamin D intake and risk of kidney stone formation cannot be used for establishing a UL for vitamin D.
- The available evidence on the relationship between vitamin D intake or status and CVD incidence or mortality cannot be used for establishing a UL for vitamin D.
- The available evidence on the relationship between vitamin D intake or status and cancer risk and mortality cannot be used for establishing a UL for vitamin D.
- The available evidence on the relationship between vitamin D intake or status and all-cause mortality cannot be used for establishing a UL for vitamin D.

Chinese Nutrition Society (CNS 2023). The CNS upheld its previously derived UL of 50 µg vitamin D per day for adults, including pregnant and lactating individuals "based on the relationship with hypercalcemia."

Indian Council of Medical Research - National Institute of Nutrition (ICMR-NIN 2020). The ICMR-NIN reviewed studies from a literature search titled "side effects of excess vitamin D intake." Based on the endpoint of vitamin D toxicity and its "hallmark" sign of increased serum 25(OH)D levels and resulting hypercalcemia, the ICMR-NIN derived an UL of 100 µg vitamin D per day for adults, including pregnant and lactating individuals.

Korean Nutrition Society (KNS 2020). The KNS published its general approach to evaluating data for setting DRI values. The KNS derived an UL value of 100 µg vitamin D per day for adults, including pregnant and lactating individuals.[6]

[6] No other information provided in English.

CRN Recommendations

The goal of this chapter was to determine whether more recent human clinical data are available that might impact the conclusions published in the 3rd edition, which derived an UL value for vitamin D of 250 µg per day (as vitamin D2 and D3).

Vitamin D without Supplemental Calcium

While not all human clinical trials are specifically designed to evaluate adverse effects, no new trials were identified following CRN's updated methodology that reported any serious adverse effects or symptoms of vitamin D toxicity associated with supplementation of vitamin D alone. As with any assessment in which not all available data are reviewed, inherent uncertainties with the risk assessment and selection of the UL are recognized. It is noteworthy that no cases of persistent hypercalcemia or hypercalciuria were observed following intervention with vitamin D alone in any RCT reviewed in this update. The evidence reviewed previously by the IOM (1998) suggesting vitamin D caused hypercalcemia came from anecdotal reports of accidental or misinformed consumption of much higher amounts.

CRN's safety methodology for deriving supplemental UL values prioritizes data from human clinical studies when available. The table below summarizes the key human clinical studies considered in deriving the supplemental UL value by CRN according to its principal points of departure for risk assessment (as described in the Methodology Chapter).[7]

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

New Studies Considered for the CRN UL for Vitamin D in Adults *without calcium co-supplementation*

Reference	Participant Description	No. of Subjects	Dose(s) of Vitamin D3	Duration (months)[a]	NOAEL (µg/day) Persistent Hypercalcemia	NOAEL (µg/day) Persistent Hypercalciuria
Ganie et al. 2023	Healthy adults with vitamin D deficiency	153	600 µg/day, 1,000 µg/day, 2,000 µg/day; 60,000 µg/month	3 consecutive months for 6 months total	2,000	2,000
Drincic et al. 2013	Healthy adults	67	25 µg/day, 125 µg/day, 250 µg/day	5 months	250	NA
Heaney et al. 2023	Healthy males	67	0, 25 µg/day, 125 µg/day, 250 µg/day	4 months	250	NA
Shirvani et al. 2020	Healthy adults	33	15 µg/day, 100 µg/day, 250 µg/day	6 months	250	NA
Guella et al. 2023	Hemodialysis patients	23	300,000 IU monthly [250 µg per day]	9 months	250	NA
Mangas-Sánchez et al. 2023	Patients with cystic fibrosis	≤15[b]	800-10,000 IU/day [20-250 µg per day]	12 months	250	NA
Takacs et al. 2023	Subjects with vitamin D deficiency	69	30,000 IU per week [107 µg/day], then 30,000 IU biweekly [53.6 µg/day]; 30,000 IU twice weekly [214.2 µg per day] then 30,000 IU biweekly [53.6 µg/day]	4.5 months	214	214

NA, not assessed

[a] Months calculated based on 4 weeks per month

[b] Fifteen patients were >10 years old, including adults; however, detailed ages were not provided.

No serious adverse effects or early markers related to potential vitamin D toxicity (e.g.,

persistent hypercalcemia or hypercalciuria) were reported in any study administering vitamin D alone (i.e., not in combination with supplemental calcium) identified as part of this update. Of the nine studies with vitamin D supplementation alone (above 200 µg per day) that assessed for the early markers of hypercalcemia and/or hypercalciuria, seven reported no persistent or transient occurrences up to the highest doses tested (see Table above).

Of note, the EFSA (2023) Panel concluded that hypercalciuria may precede hypercalcemia but noted that none of the RCTs of vitamin D alone at 250 µg per day (or higher) assessed urinary calcium. Since the EFSA's review, one new study assessed both serum and urinary calcium following administration of up to 2,000 µg vitamin D per day for a total of 12 weeks (six consecutive weeks each session) (Ganie et al. 2023). The study authors reported no incidence of hypercalcemia up to the highest dose administered, and only cases of transient hypercalciuria at 2,000 µg per day. No persistent hypercalciuria was reported at doses up to 2,000 µg per day, the highest dose administered in this study (Ganie et al. 2023). It is worth noting that, similarly to the outcome of the Ganie et al. study, no cases of hypercalcemia or hypercalciuria were identified at doses up to 214 µg per day in the study by Takacs et al. (2023).

Based on the updated available data, 250 µg per day is carried forward as the supplemental NOAEL for vitamin D without co-supplementation with calcium for adults following the CRN process. Consistent with CRN's methodology, an UF of 1 is applied to yield an UL of 250 µg (10,000 IU) per day for supplemental vitamin D in adults *when there is no co-supplementation with calcium.*

This UL does not apply to patients with medical conditions that increase the risk of hypercalcemia caused by vitamin D intake (primary hyperparathyroidism, sarcoidosis, mycobacterium infections such as tuberculosis, lymphoma, or idiopathic hypercalcemia). These individuals should consult with their healthcare provider before taking vitamin D supplements.

Vitamin D with Supplemental Calcium

As discussed in the *Safety Considerations* section, vitamin D toxicity, including the occurrence of hypercalcemia and hypercalciuria, depend on several factors, including age, salt intake, pre-

existing medical conditions, medications, and especially calcium intake (Tebben et al. 2016; Das et al. 2023). The amount (i.e., efficiency) of calcium absorption in the intestines is inversely related to dietary calcium intake (EFSA 2023). Given the established influence of calcium intake on vitamin D toxicity, including hypercalciuria, co-supplementation with calcium should be considered when establishing an UL for vitamin D. This is further supported by the Aloia et al. (2018) study, which that demonstrated calcium intake was statistically significant when assessed in the model as a time-varying covariate for occurrence of hypercalciuria.

The EFSA (2023) recently determined its UL for vitamin D intake (from all sources) to be 100 µg per day based on two studies in which 250 µg vitamin D per day co-administered with calcium was associated with hypercalciuria but not hypercalcemia (Aloia et al. 2018; Billington et al. 2020). Of the nine studies reviewed by CRN as part of the current update that analyzed for hypercalcemia and/or hypercalciuria following vitamin D plus calcium co-supplementation in doses greater than 100 µg vitamin D per day, no cases of persistent hypercalcemia were reported (Mastaglia et al. 2006; Jorde et al. 2008; Grimnes et al. 2012; Gallagher et al. 2012, 2013; Burnett-Bowie et al. 2012; Rafii et al. 2019; Aloia et al. 2018; Billington et al. 2020). Only the same two studies identified by the EFSA (2023) reported persistent hypercalciuria (Aloia et al. 2018; Billington et al. 2020). Of note, these are the only two studies across the 19 studies that investigated vitamin D supplementation with or without calcium co-supplementation that reported any persistent effects (i.e., hypercalciuria) in patients.

As discussed herein, the methodologies utilized in the Billington et al. (2020) and Aloia et al. (2018) studies raise questions about the utility of their findings. First, the OR for incidence of hypercalciuria in the 250 µg per day group as compared to the 10 µg per day group was found to be 3.0 by Billington et al. (2020); however, the authors did not correct 24-hour urinary calcium for creatinine. Similarly, the crude OR for incidence of hypercalciuria in the 250 µg per day group compared to the 15 µg per day group was found to be 2.8 by Aloia et al. (2018); however, the authors used a cut-off of 250 mg per day urine calcium. If the authors had applied a cut-off of 300 mg per day (as was done in some other studies), the creatinine corrected 24-urinary calcium levels reported in by Aloia et al. (2018) would not be identified as elevated (i.e., hypercalciuria).

In addition, diagnosis of hypercalcemia mediated by vitamin D excess is typically based on the occurrence of elevated serum calcium (i.e., hypercalcemia) and certain vitamin D metabolite concentrations together with reduced PTH (Tebben et al. 2016). Therefore, the selection of hypercalciuria as the basis of an UL for vitamin D toxicity is inherently conservative, as it is an early potential marker of vitamin D toxicity that has also been shown to be reversible (EFSA 2023). However, the significantly reduced PTH concentrations in participants during hypercalciuria episodes reported by Billington et al. (2020) provides support that the vitamin D-mediated hypercalcemia pathway was perturbed in that study. In addition, the mean (SD) serum 25(OH)D concentrations were found to be 198 (42) nmol/L and 216 (66) nmol/L in the 250 µg per day group of Billington et al. (2020) and Aloia et al. (2018), respectively. These serum 25(OH)D levels fall within the range thought to be associated with potential vitamin D toxicity (i.e., > 200 nmol/L).

In addition to Billington et al. (2020) and Aloia et al. (2018), only four other studies assessed hypercalciuria as a side effect when vitamin D was administered alongside calcium. Two studies reported no persistent hypercalcemia at 120 µg vitamin D per day (Gallagher et al. 2012, 2013) while two studies were determined to have unclear findings at 250 µg per day and 357 µg vitamin D per day, respectively (Mastaglia et al. 2006; Rafii et al. 2019).

Taken together, the available data are insufficient to establish an UL for co-supplementation of vitamin D and calcium. As such, individuals should consult with their healthcare provider before taking vitamin D supplements concurrently with calcium supplements. As this area of research continues to grow, additional data may become available that could warrant revision of this assessment.

Quantitative Summary for Vitamin D (as D2 or D3) in Adults

CRN UL (2026), supplemental intake	250 µg (10,000 IU)/day *without calcium co-supplementation*[a] Not determined for vitamin D *with calcium co-supplementation*[a]
IOM (2011) UL, total intake	100 µg (4,000 IU)/day
EFSA (2023) UL, total intake	100 µg VDE (4,000 IU)/day
EVM (2003), guidance level, supplemental intake	25 µg (1,000 IU)/day
CNS (2023), total intake	50 µg (2,000 IU)/day
ICMR-NIN (2020), total intake	100 µg (4,000 IU)/day
KNS (2020), total intake	100 µg (4,000 IU)/day

VDE, vitamin D equivalent

[a] Excludes patients with certain medical conditions that can increase the risk of hypercalcemia caused by vitamin D intake (primary hyperparathyroidism, sarcoidosis, mycobacterium infections such as tuberculosis, lymphoma, or idiopathic hypercalcemia). These individuals should consult with their healthcare provider when planning to supplement with vitamin D.

References

Aloia JF, Dhaliwal R, Shieh A, Mikhail M, Islam S, Yeh JK. 2013. Calcium and vitamin D supplementation in postmenopausal women. J Clin Endocrinol Metab. 98(11):E1702-9.

Aloia JF, Katumuluwa S, Stolberg A, Usera G, Mikhail M, Hoofnagle AN, Islam S,.2018. Safety of calcium and vitamin D supplements, a randomized controlled trial. *Clin Endocrinol*. 89, 742–749.

Aranow C. 2011. Vitamin D and the immune system. *Journal of Investigative Medicine*, the official publication of the American Federation for Clinical Research. 59(6), 881–886.

Armas LA, Hollis BW, Heaney RP. 2004. Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab*. 89(11):5387-5391.

Balachandar R, Pullakhandam R, Kulkarni B, Sachdev HS. 2021. Relative efficacy of vitamin D2 and vitamin D3 in improving vitamin d status: systematic review and meta-analysis. *Nutrients*. 13(10):3328.

Barger-Lux MJ, Heaney RP, Dowell S, Chen TC, Holick MF. 1998. Vitamin D and its major metabolites: serum levels after graded oral dosing in healthy men. *Osteoporosis Int*. 8:222–230.

Billington EO, Burt LA, Rose MS, Davison EM, Gaudet S, Kan M, Boyd SK, Hanley DA. 2020. Safety of highdose vitamin D supplementation: secondary analysis of a randomized controlled trial. *J Clin Endocrinol Metab*. 105, 1261–1273.

Bikle DD. Vitamin D: Production, Metabolism, and Mechanism of Action. 2025. In: Feingold KR, Adler RA, Ahmed SF, Anawalt B, Blackman MR, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hamilton E, Hofland J, Jan de Beur S, Kalra S, Kaltsas G, Kapoor N, Kim M, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Muzumdar R, Purnell J, Rey R, Sahay R, Shah AS, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–.

Borel P, Caillaud D, Cano N. 2015. Vitamin D Bioavailability: State of the Art. *Crit Rev Food Sci Nutr*. 55(9):1193-1205.

Bowman CA, Bichoupan K, Posner S, Schonfeld E, Pappas A, Woodward M, Schiano T, Branch AD. 2024. A prospective open-label dose-response study to correct vitamin D deficiency in cirrhosis. *Dig Dis Sci*. 69:1456–1465.

Brohult J and Jonson B. 1973. Effects of large doses of calciferol on patients with rheumatoid arthritis. A doubleblind clinical trial. *Scand J Rheumatol*. 2:173–176.

Brown EIG, Darling AL, Robertson TM, et al. 2025. Effect of vitamin D2 supplementation on 25-

hydroxyvitamin D3 status: a systematic review and meta-analysis of randomized controlled trials. *Nutr Rev*. Published online September 18, 2025. doi:10.1093/nutrit/nuaf166.

Burnett-Bowie SAM, Leder BZ, Henao MP, Baldwin CM, Hayden DL and Finkelstein JS. 2012. Randomized trial assessing the effects of ergocalciferol administration on circulating FGF23. *CJSAN*. 7:624–631.

Ceglia L, Niramitmahapanya S, da Silva Morais M, Rivas DA, Harris SS, Bischoff-Ferrari H, Fielding RA, Dawson-Hughes B. 2013. A randomized study on the effect of vitamin D_3 supplementation on skeletal muscle morphology and vitamin D receptor concentration in older women. *J Clin Endocrinol Metab*. 98(12):E1927-35.

Chinese Nutrition Society (CNS). 2023. *Dietary Reference Intakes for China, A summary Report.* People's Medical Publishing House.

Das L, Holick MF, Sachdeva N, Bhadada SK, Singhmar S, Thakur N, Dutta P, Marwaha RK. 2023. Efficacy, safety, and dose-response effects of calcifediol supplementation on 25-hydroxyvitamin D, parathyroid hormone, and 1,25-dihydroxyvitamin D levels in healthy adults: An open-label interventional pilot study. *Indian J Pharmacol*. 55:101–107.

Delage B. 2017. Vitamin D webpage. Linus Pauling Institute website. https://lpi.oregonstate.edu/mic/vitamins/vitamin-D. (Updated July 2017; Reviewed October 2017).

Diamond T, Wong YK, Golombick T. 2013. Effect of oral cholecalciferol 2,000 versus 5,000 IU on serum vitamin D, PTH, bone and muscle strength in patients with vitamin D deficiency. *Osteoporos Int*. 24(3):1101-5.

Dominguez LJ, Farruggia M, Veronese N, Barbagallo M. 2021. Vitamin D Sources, Metabolism, and Deficiency: Available Compounds and Guidelines for Its Treatment. *Metabolites*. 11(4):255.

Drincic A, Fuller E, Heaney RP, Armas LA. 2013. 25-Hydroxyvitamin D response to graded vitamin D3 supplementation among obese adults. *J Clin Endocrinol Metab.* 98, 4845–4851.

Dudenkov DV, Yawn BP, Oberhelman SS, Fischer PR, Singh RJ, Cha SS, Maxson JA, Quigg SM, Thacher TD. 2015. Changing Incidence of Serum 25-Hydroxyvitamin D Values Above 50 ng/mL: A 10-Year Population-Based Study. *Mayo Clin Proc*. 90(5):577-86.

Durrant LR, Bucca G, Hesketh A, et al. 2022. Vitamins D2 and D3 have overlapping but different effects on the human immune system revealed through analysis of the blood transcriptome. *Front Immunol*. 3:790444.

Enkhmaa D, Tanz L, Ganmaa D, Enkhtur S, Oyun EB, Stuart J, Chen G, Carr A, Seely EW, Fitzmaurice G, Buyandelger Y, Sarantsetseg B, Gantsetseg G, Rich EJ. 2019. Randomized trial of three doses of vitamin D to reduce deficiency in pregnant Mongolian women. *eBioMedicine*. 39:10–519.

European Food Safety Authority (EFSA). 2012. EFSA Panel on Dietetic Products, Nutrition and

Allergies (NDA); scientific opinion on the tolerable upper intake level of vitamin D. *EFSA J.* 10(7):2813.

European Food Safety Authority (EFSA). 2023. EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA). Scientific opinion on the tolerable upper intake level for vitamin D, including the derivation of a conversion factor for calcidiol monohydrate. *EFSA J*. 21(8):8145.

Expert Group on Vitamins and Minerals (EVM), Committee on Toxicity. 2003. *Safe Upper Levels for Vitamins and Minerals*. London: Food Standards Agency Publications.

Gallagher JC, Sai A, Templin T 2nd, Smith L. 2012. Dose response to vitamin D supplementation in postmenopausal women: a randomized trial. *Ann Intern Med*. 20;156(6):425-37. Erratum in: *Ann Intern Med*. 2012 May 1;156(9):672.

Gallagher JC, Peacock M, Yalamanchili V, Smith LM. 2013.Effects of vitamin D supplementation in older African American women. *J Clin Endocrinol Metab*. 2013. 98(3):1137-46.

Ganie MA, Sidana S, Baba MS, Sahar T, Rashid A, Asrar MM, Marwaha RK, Wani IA, Misgar, RA, Wani, I.A. 2023. Efficacy and safety of various oral regimens (three oral doses) and schedules (daily v. monthly) of cholecalciferol in North Indian adults with low vitamin D status: evidence from a randomised controlled trial. *Br J Nutr*. 129(10), 1732-1739.

Grimnes G, Joakimsen R, Figenschau Y, Torjesen PA, Almås B, Jorde R. 2012. The effect of high-dose vitamin D on bone mineral density and bone turnover markers in postmenopausal women with low bone mass--a randomized controlled 1-year trial. *Osteoporos Int*. 23(1):201-11.

Guella A, Abduelkarem AR, Hassanein MM. 2023. The effects and safety of high dose vitamin D3 in hemodialysis patients. *Pharmacy Practice*. 21(1):2773.

Hathcock JN, Shao A, Vieth R, Heaney R. 2007. Risk assessment for vitamin D. *Am J Clin Nutr*. 85:6–18.

Heaney RP, Davies KM, Chen TC, et al. 2003. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr*. 77: 204–210.

Hin H, Tomson J, Newman C, Kurien R, Lay M, Cox J, Sayer J, Hill M, Emberson J, Armitage J, Clarke R. 2016. Optimum dose of vitamin D for disease prevention in older people: BEST-D trial of vitamin D in primary care. *Osteoporos Int*. 28(3):841-851. Erratum in: *Osteoporos Int*. 2025 Jul;36(7):1293.

Holden RM, Norman PA, Day AG, Silver SA, Clemens KK, Iliescu E. 2024. Vitamin D status and treatment in ESKD: Links to improved CKD-MBD laboratory parameters in a real-world setting. *Am J Nephrol*. 55:285–294.

Holick MF. 1996. Vitamin D and bone health. *The Journal of Nutrition*. 126(4 Suppl), 1159S–64S.

Holick MF. 1999. Vitamin D. In: Shils ME, Olson JA, Shike M, eds. *Modern Nutrition in Health and Disease.* 8th ed. Philadelphia: Lea and Febiger; 8–25.

Holick MF. 2015. Vitamin D Is Not as Toxic as Was Once Thought: A Historical and an Up-to-Date Perspective. *Mayo Clin Proc*. 90(5):561-4.

Hollis BW, Wagner CL. 2004. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. *Am J Clin Nutr.* 80:1752S–1758S.

Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. 2011. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. *J Bone Miner Res.* 26:2341–2357.

Indian Council of Medical Research - National Institute of Nutrition (ICMR-NIN). 2020. *ICMR-NIN Expert Group on Nutrient Requirement for Indians, Recommended Dietary Allowances (RDA) and Estimated Average Requirements (EAR)*.

Institute of Medicine (IOM). 2011. *Dietary Reference Intakes: Calcium, Vitamin D*. Washington, DC: National Academies Press.

Jódar-Gimeno E, Pérez-Castrillón JL, Nociar J, Lojka M, Nikolov D, Cereto-Castro F, Novković S, Tarantino U, Mehsen-Cetre N, Arranz P, Ostalé CM, García-Bea A, Gilaberte I. 2024. Efficacy and safety of weekly calcifediol formulations (75 and 100 µg) in subjects with vitamin D deficiency: A phase II/III randomized trial. *Nutrients*. 16:421.

Johnson KR, Jobber J, Stonawski BJ. 1980. Prophylactic vitamin D in the elderly. *Age and Ageing.* 9:121–127.

Johnson KC, Pittas AG, Margolis KL, Peters AL, Phillips LS, Vickery EM, Nelson J, Sheehan PR, Reboussin D, Malozowski S, Chatterjee R; D2d research group. 2022. Safety and tolerability of high-dose daily vitamin D_3 supplementation in the vitamin D and type 2 diabetes (D2d) study-a randomized trial in persons with prediabetes. *Eur J Clin Nutr*. 76(8):1117-1124. Erratum in: *Eur J Clin Nutr.* 2022 Oct;76(10):1491.

Jones KS, Assar S, Harnpanich D, et al. 2014. 25(OH)D2 half-life is shorter than 25(OH)D3 half-life and is influenced by DBP concentration and genotype. *J Clin Endocrinol Metab*. 99(9):3373-3381.

Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K. 2008. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. *J Intern Med*. 264(6):599-609.

Korean Nutrition Society (KNS). 2020. Ministry of Health and Welfare (KR). The Korean Nutrition Society. *Dietary Reference Intakes for Koreans*. Sejong: Ministry of Health and Welfare.

Mangas-Sánchez C, Garriga-García M, Serrano-Nieto MJ, Garcia-Romero R, Beltrán MÁ, Crehuá-Gaudiza E, Vicente-Santamaría S, Martínez-Costa C, Díaz-Martín JJ, Bousoño-García C, González-Jiménez D. 2023. Safety and efficacy of a new supplementation protocol in patients with cystic fibrosis and vitamin D deficiency. *Anales de Pediatría* (English Edition). 98(4):257-266.

Mastaglia SR, Mautalen CA, Parisi MS, Oliveri B. 2006. Vitamin D2 dose required to rapidly increase 25OHD levels in osteoporotic women. *Eur J Clin Nutr*. 60(5):681-7.

Miller DR, Hayes KC. 1982. Vitamin excess and toxicity. In: Hathcock JN, ed. *Nutritional Toxicology.* Vol. 1. New York: Academic Press; 81–133.

National Institutes of Health (NIH). 2025. Vitamin D Fact Sheet for Health Professionals. https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/.

Oliveri B, Mastaglia SR, Brito GM, et al. 2015. Vitamin D3 seems more appropriate than D2 to sustain adequate levels of 25OHD: a pharmacokinetic approach. *Eur J Clin Nutr*. 69(6):697-702.

Ponda MP, Dowd K, Finkielstein D, Holt PR, Breslow JL. 2012. The short-term effects of vitamin D repletion on cholesterol: a randomized, placebo-controlled trial. *Arterioscler Thromb Vasc Biol*. 32(10):2510-5.

Porto C, Petribu K, Barbosa N, Magalhães R, Lira C, Porto AB, Markman-Filho B, Lordsleem A, Calado E, Magalhães J, Sougey E, Silva T, Junio A, Bandeira F, Leão R. 2025. Randomized, placebo-controlled, double-blind clinical trial on the contributions of vitamin D in the control of cardiovascular risk factors, depressive symptoms and suicide risk. *Am Heart J Plus*. 37:100351.

Rafii DC, Ali F, Farag A, Iyer B, Otterbeck PE, Chaudhari R, Potter N, Stefanov DG, Guber HA. 2019. A prospective study of commonly utilized regimens of vitamin d replacement and maintenance therapy in adults. *Endocr Pract*. 25(1):6-15.

Ramot R, Yadav S, Vishnoi SK, Sharma P, Khadgawat R, Jora R. 2022. Effect of maternal supplementation with two different doses of vitamin D during lactation on vitamin D status, anthropometry and bone mass of infants: A randomized controlled trial. *Indian Pediatr*. 59, 276–282.

Rorie A, Goldner WS, Lyden E, Poole JA. 2014. Beneficial role for supplemental vitamin D3 treatment in chronic urticaria: a randomized study. *Ann Allergy Asthma Immunol*. 112(4):376-82.

Roth DE, Morris SK, Zlotkin S, Gernand AD, Ahmed T, Shanta SS, Papp E, Korsiak J, Shi J, Islam MM, Jahan I, Keya FK, Willan AR, Weksberg R, Mohsin M, Rahman QS, Shah PS, Murphy KE, Stimec J, Pell LG, Qamar H, al Mahmud A. 2018. Vitamin D supplementation in pregnancy and lactation and infant growth. *NEJM*. 379, 535–546.

Shah R, Das L, Bansal D, Sachdeva N, Holick MF, Dutta P, Medenica S, Marwaha RK. 2025. An open-label interventional study on efficacy and safety of 25 µg of daily calcifediol capsule versus 100 µg of cholecalciferol sachets in apparently healthy volunteers. *J Nutr Sci*. 14:e18.

Shirvani A, Kalajian TA, Song A, Allen R, Charoenngam N, Lewanczuk R, Holick MF. 2020. Variable genomic and metabolomic responses to varying doses of vitamin D supplementation. *Anticancer Research*. 40, 535–543.

Schwartz JB, Kane L, Bikle D. 2016. Response of Vitamin D Concentration to Vitamin D3 Administration in Older Adults without Sun Exposure: A Randomized Double-Blind Trial. *J Am Geriatr Soc*. 64(1):65-72.

Takacs I, Bakos B, Nemeth Z, Toth BE, Szili B, Lakatos P. 2023. Controlled randomized open label clinical study comparing the safety and efficacy of loading schedules in vitamin D deficient patients. *J Steroid Biochem Mol Biol*. 231:106330.

Tebben PJ, Singh RJ, Kumar R. 2016. Vitamin D-Mediated Hypercalcemia: Mechanisms, Diagnosis, and Treatment. *Endocr Rev*. 37(5):521-547.

Thouvenot E, Laplaud D, Lebrun-Frenay C, Derache N, Le Page E, Maillart E, Froment-Tilikete C, Castelnovo G, Casez O, Coustans M, Guennoc AM, Heinzlef O, Magy L, Nifle C, Ayrignac X, Fromont A, Gaillard N, Caucheteux N, Patry I, De Sèze J, Deschamps R, Clavelou P, Biotti D, Edan G, Camu W, Agherbi H, Renard D, Demattei C, Fabbro-Peray P, Mura T, Rival M. 2025. High-dose vitamin D in clinically isolated syndrome typical of multiple sclerosis: The D-Lay MS randomized clinical trial. *JAMA*. 333:135–145.

Trang HM, Cole DE, Rubin LA, Pierratos A, Siu S, Vieth R. 1998. Evidence that vitamin D3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D2. *Am J Clin Nutr*. 68(4):854-858.

Tripkovic L, Lambert H, Hart K, et al. 2012. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. *Am J Clin Nutr*. 95(6):1357-1364.

Tripkovic L, Wilson LR, Hart K, et al. 2017. Daily supplementation with 15 μg vitamin D2 compared with vitamin D_3 to increase wintertime 25-hydroxyvitamin D status in healthy South Asian and white European women: a 12-wk randomized, placebo-controlled food-fortification trial. *Am J Clin Nutr*. 106(2):481-490.

Vieth R, Chan P, MacFarlane GD. 2001. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr*. 73:288–294.

Wagner CL, Hulsey TC, Fanning D, Ebeling M, Hollis BW. 2006. High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. *Breastfeed Med*. 1(2):59-70.

Wagner H, Alvarsson M, Mannheimer B, Degerblad M, Östenson CG. 2016. No Effect of High-Dose Vitamin D Treatment on β-Cell Function, Insulin Sensitivity, or Glucose Homeostasis in Subjects with Abnormal Glucose Tolerance: A Randomized Clinical Trial. *Diabetes Care*. 39(3):345-52.

Wamberg L, Pedersen SB, Richelsen B, Rejnmark L. 2013. The effect of high-dose vitamin D supplementation on calciotropic hormones and bone mineral density in obese subjects with low levels of circulating 25-hydroxyvitamin d: results from a randomized controlled study. *Calcif Tissue Int.* 93(1):69-77.

Updated July 2026 by

ToxStrategies, LLC, a BlueRidge Life Sciences Company