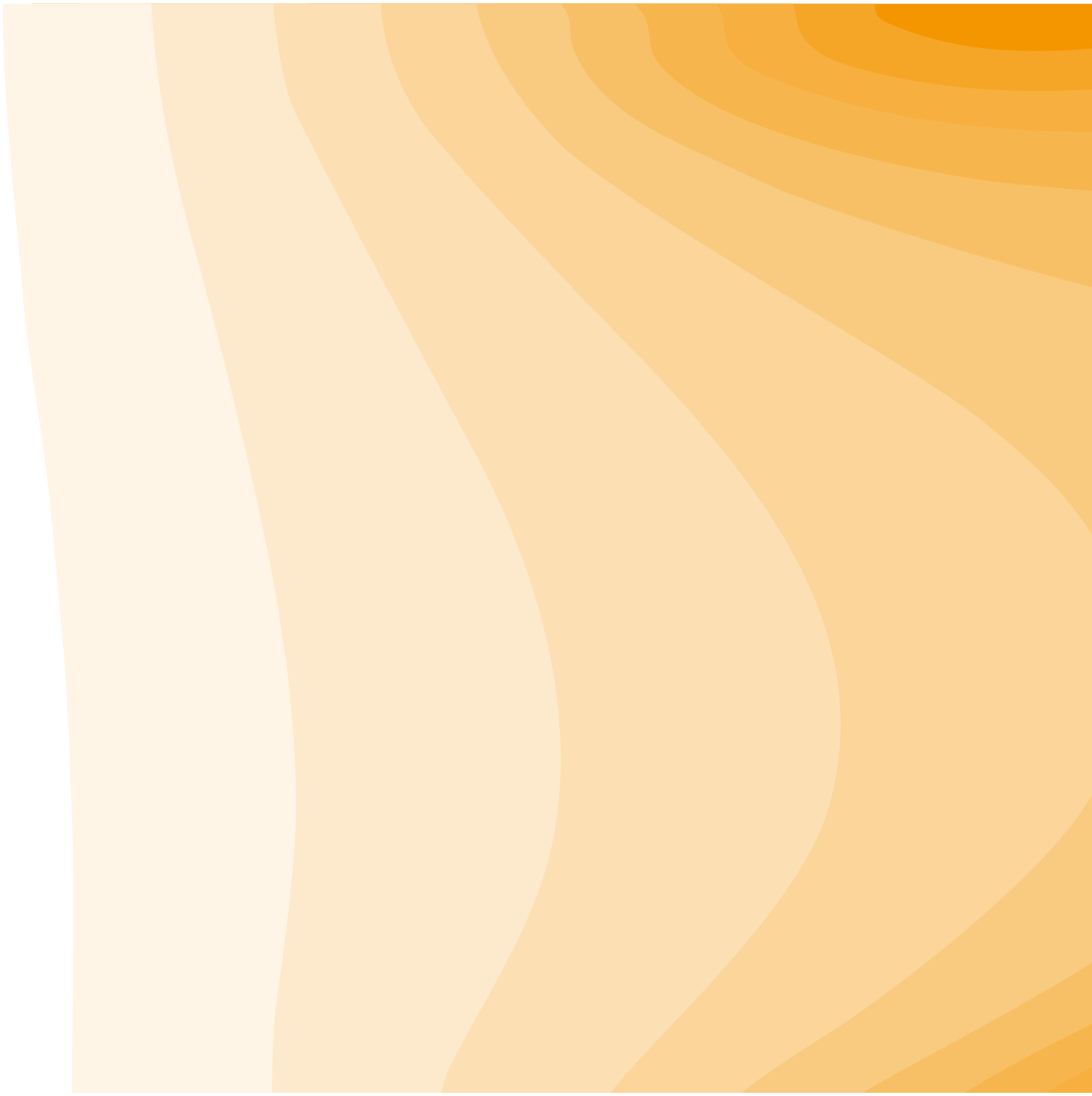
The Updated Risk Assessment of Vitamin D



IADSA
International Alliance of Dietary/
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The International Association of Dietary/Food Supplement Associations (IADSA) brings together over 50 associations of dietary/food supplement manufacturers and distributors from across the world. IADSA's central goal is to ensure a greater exchange of information about the science and regulation of dietary supplements and ingredients among scientists, regulators, industry and consumers.

'The Updated Risk Assessment of Vitamin D' has been researched and developed by IADSA Scientific Group members Dr. Andrew Shao PhD and Dr. John Hathcock PhD, assisted by Ms Haiuyen Nguyen.

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Background

The literature on vitamin D has rapidly evolved in recent years, with a variety of both well documented and emerging health benefits now identified. In addition to its well established effects on bone, human data now suggest that vitamin D may provide benefits related to the risk for certain cancers (1-4), autoimmune disorders (5), diabetes (6), cardiovascular disease (2, 7, 8), dementia (9), and even longevity (10, 11) and total mortality (12-14). The amounts of vitamin D needed to produce these various beneficial effects (25+ µg per day equivalent) are greater than that previously thought nutritionally sufficient (5 – 10 µg per day or 15 µg in older persons). The Adequate Intake (AI) identified by the US Institute of Medicine (IOM) (5 – 15 µg; 200 – 600 IU per day for adults ≥19 years) is based on older and now outdated evidence (15).

Coinciding with these new findings has been the reemergence of the overt deficiency disease rickets in developed countries (16), which had previously thought to have rid themselves of such problems. Globally, a decline in vitamin D status (as reflected by lower serum 25-hydroxyvitamin D, 25(OH)D levels) over the past several decades has now been documented (17-21), with mean 25(OH)D levels well below what is now considered optimal (22). Most experts believe this optimal range to be 75 – 100 nmol/L (23, 24). In contrast, recent surveys indicate that typical mean serum 25(OH)D levels range from 30 – 60 nmol/L (18, 20, 25). The factors responsible for the decline in vitamin D status likely include but may not be limited to geographic location (26), societal efforts to avoid sun exposure due to skin cancer concerns (27), technological advances limiting sun exposure, obesity (28, 29), other social and cultural influences, and the limited availability of vitamin D-rich foods (30, 31).

The convergence of data suggesting multiple health benefits in the form of reduced chronic disease risk from improved vitamin D status, combined with compelling data indicating substantial vitamin D inadequacy in North America, has recently prompted the US and Canadian governments to undertake the process of revising the calcium and vitamin D Dietary Reference Intakes (DRIs)[1]. The DRIs are a set of values that include recommended intake levels for various age-gender groups and pregnant and lactating women. Also included in the DRIs is the tolerable upper intake level, or UL, an intake defined to be safe. The UL is defined as the highest level of intake likely to pose no risk of adverse health effects for almost all individuals in the general population (32).

Notes

1 Dietary Reference Intakes for Vitamin D and Calcium. Food and Nutrition Board, Institute of Medicine, National Academies of Science. http://www.iom.edu/CMS/3788/61170.aspx

Relying on a risk assessment model first introduced by the IOM (32), several authoritative bodies have established ULs for vitamin D (IOM; 50 µg or 2000 IU per day (15); European Commission Scientific Committee on Food (SCF); 50 µg (33); United Kingdom Expert Group on Vitamins and Minerals (EVM); 25 µg (34). These values are now widely recognized as being far more restrictive than needed to avoid adverse effects of vitamin D, are outdated and superseded by more recent data.

The evolution of the human dataset relevant to vitamin D safety has been as rapid as that for efficacy. In the past decade, a large number of well designed human clinical trials have been published involving relatively high doses of vitamin D in a range of populations and subgroups. These data, combined with a general scientific consensus of serum 25(OH)D levels as the marker for vitamin D status, have drastically informed our knowledge regarding the safety of vitamin D. The last published risk assessment of vitamin D concluded that up to 250 µg (10,000 IU) vitamin D per day is safe for most healthy adults and that this value should be identified by officials as the revised UL (35). Presented here is an updated risk assessment of vitamin D based on the most recently published human clinical trials. Based on these data, there is no compelling reason to adjust the 250 µg value upward or downward, and this should stand as the recommended UL for vitamin D.

Methods

The most recent publication of a vitamin D risk assessment using the safe tolerable upper intake level (UL) method was published in 2007 (35). Previous risk assessments using the UL method have also been published by the FNB (15), the Scientific Committee on Food of the European Commission (33), and the Expert Group on Vitamins and Minerals of the United Kingdom (34). The UL method involves three basic, standardized steps (32):

1. Hazard identification

The evaluation of all pertinent information relative to the substance's potential to cause harm in humans. This step identifies the nature of the adverse effect, including its severity and persistence. If the substance causes multiple types of adverse effects, the critical effect is one that meets the severity and persistence criteria at the lowest intake.

2. Dose-response assessment

A quantitative evaluation of the relationship between oral intake of the nutrient and any adverse effects that result. The No Observed Adverse Effect Level (NOAEL) and, if possible, the Lowest Observed Adverse Effect Level (LOAEL) are identified, and the degree and type of uncertainty is assigned a numerical value, the uncertainty factor (UF).

3. Derivation of the UL

A simple arithmetic operation: UL = NOAEL ÷ UF (or sometimes UL = LOAEL ÷ UF).

The hazard identification includes consideration of the evidence for causality. The dose-response assessment considers sensitive subpopulations and judgment of the uncertainty in the data related to the critical effect (32). The dose-response relationship evaluation could be done with a high degree of uncertainty about the dosage that qualifies as a NOAEL, or cautiously to identify a lower dosage that carries a low degree of uncertainty about qualifying as a NOAEL.

The usual approach to uncertainty involves identifying the highest NOAEL supported by the data, and judging the strengths and extent of the available data to select a numerical UF to be used in calculating the UL. The size of the UF depends on the robustness of the data used to identify the NOAEL, the severity and persistence of the critical effect, and the strengths and amount of supporting data. The factors that impact the UF are widely accepted but there are no specific or widely accepted criteria used to derive the exact UF values. Indeed, the overall UF values that have been selected and applied by the IOM to the various nutrients range from 1 to 5 for human datasets, and up to 300 for animal data, with each of these being the product of several independent factors for different data characteristics (15, 36-38).

To avoid the seemingly arbitrary aspects of UF selection, an alternative approach to select a NOAEL or Observed Safe Level (39) or Highest Observed intake (40) (OSL or HOI) value that justifies use of a UF of 1.0 has been developed for application to human clinical trial datasets. Regardless of the approach - with either the usual treatment of uncertainty or this alternative approach - qualitative scientific judgment is required. However, the alternative avoids the quantitative judgment required to select a specific numerical value for the UF. The new approach involves arrangement of the clinical trial dataset in decreasing order of intake of a substance, identification of those trials that produced no adverse effects (provisional NOAEL values) and selection downward until the dataset is judged strong enough to justify application of UF = 1.0, with the consequent that the selected NOAEL (or OSL or HOI) equals the UL (i.e., NOAEL ÷ 1). Uncertainty related to the selected NOAEL is decreased by the absence of adverse effects in trials at higher intakes (each providing a higher provisional NOAEL value) that alone are not of sufficient scientific strength to justify UF = 1.0.

Vitamin D_2 vs. vitamin D_3

Many vitamin D-containing dietary supplements and fortified foods contain the vitamin D_3 form (cholecalciferol) while others contain the vitamin D_2 form (ergocalciferol), the latter sourced from plants. Similarly, some clinical trials have tested the D_3 form while others included the D_2 form. There has been speculation in the literature that the D_2 form is less potent due to its more rapid clearance from the body (41, 42). This assertion appears to have been based on studies involving the administration of bolus (single) doses (43). Longer-term trials involving chronic (daily) administration indicate that at a given dosage, the D_2 form is as effective at raising and maintaining serum 25(OH)D levels as the D_3 form (44). There are no convincing reports in the literature that establish separate safety profiles for the two forms. Therefore, because the UL is based on chronic exposure, for the purposes of this risk assessment, D_2 and D_3 are considered equivalent and the conclusions that follow can be applied to either form.

Clinical trial evidence

The overall body of evidence from well-conducted human intervention trials is judged to be sufficient to select a NOAEL value, and thus animal data will not be reviewed. The clinical trials are considered in order of decreasing daily dosages of vitamin D, in order to make clear the procedure and criteria for selection of a NOAEL that warrants a high level of confidence and application of a UF of 1.0. Newer clinical trials published subsequent to the 2007 risk assessment (35) are listed and briefly described in Table 1. The primary criterion for study inclusion was the same as that previously used in 2007 (use of a vitamin D dose substantially above the current Adequate Intake (AI) (≥45 µg, 1,800 IU/d), followed by study design (e.g. randomized, controlled, duration and sample size). Uncontrolled trials and those involving administration of vitamin D bolus doses and parenteral (non-oral) administration are also included in Table 1, but provide little-to-no impact on the final conclusions. Relevant outcomes once again include statistically significant changes in serum 25(OH)D (the accepted marker of vitamin D status), increases in urinary and/or serum calcium and other adverse effects.

7,500 µg/day (300,000 IU)

Two studies have been published since 2007 involving a vitamin D dose of 7,500 µg/day, both of which involved bolus dosing and both were uncontrolled trials (45, 46). While no hypercalcemia was observed in either study, neither is appropriate for use in revising the NOAEL.

2,500 µg/day (100,000 IU)

One small study was published involving a 2,500 µg/day dose in healthy adults (47). The study was randomized and controlled but involved a bolus dose. No hypercalcemia was observed, but the study is not appropriate for use in revising the NOAEL.

1,250 µg/day (50,000 IU)

One small study was published involving multiple sclerosis patients who received vitamin D dose of 1,250 µg/day for 10 days followed by a lower dose of 178 µg/day for 3 months (48). A significant increase in serum 25(OH)D to 116 nmol/L was reported, but neither serum nor urinary calcium was measured. While there were no adverse effects reported, the short duration of the study in a diseased population argues against the use of this study for revising the NOAEL. The trial by Heaney et al. (49) continues to serve as the basis of the NOAEL identified in the previous risk assessment (250 µg/day), and this selection is not altered by newer published clinical trials. However, confidence is gained in this value by data from additional clinical trials at higher doses and the absence of adverse effects at lower doses (50-66) (Table 1).

The possible adverse effect of increased serum calcium with a daily oral dose of 95 µg in one study (67) (the basis of the current FNB UL) continues to be inconsistent with the totality of the evidence, suggesting that some mistake, perhaps in the identification of the administered vitamin D dosage, may have occurred. Further, the absence of serum 25(OH)D measurement in this study makes it impossible to confirm the reported vitamin D dosages.

Case reports

There continue to be reports published in the literature of accidental or uninformed consumption of very high levels of vitamin D associated with symptoms of toxicity (severe hypercalcemia and other accompanying side effects) (Table 2) (68-89). The ability to draw firm conclusions on dose-response effects is limited, due to the heterogeneous nature of the data and lack of adequate controls. Important details such as dose, duration of exposure and serum 25(OH)D are often missing from published case reports. Furthermore, of the reported cases of vitamin D toxicity, nearly all have involved patients with compromised health, especially renal insufficiency, or confounding by hydrochlorothiazide treatment or other factors, limiting the relevance to the generally healthy population.

The majority of cases exhibiting toxicity presented with serum 25(OH)D levels ranging from 375 (68) to over 3,700 nmol/L (82). The few case reports in which patients presented with serum 25(OH)D levels close to, or below that achieved with the recommended NOAEL (250 µg per day, 220 nmol/L) (49) can be explained as follows. Taskapan reported toxicity (serum calcium 3.44 mmol/L) in a 77 year-old woman who had been ingesting 1,250 µg (50,000 IU)/day vitamin D_2 for more than 2 years (71). Serum 25(OH)D was reported to exceed 250 nmol/L, but the authors also pointed out that the vitamin D toxicity was exacerbated by the presence of primary hyperparathyroidism in this patient. Chan reported symptoms of vitamin D toxicity (serum calcium 3.54 mmol/L) that was accompanied by a serum 25(OH)D of 175 nmol/L in a 10 month-old girl (78). The vitamin D dose was unknown. These two cases clearly are not relevant to generally healthy adults.

There is one published case report of an 85 year-old woman experiencing hypercalcemia and other adverse effects from a relatively low dose of vitamin D_3 (10 µg (400 IU)/day for 2 mo) (88). The serum 25(OH)D level upon admission was 62 nmol/L, well below that believed to be associated with toxicity. This is clearly an anomalous finding, and suggests a reporting error of some kind and/or concomitant use of medications that may have affected the observations.

There are also case reports in the published literature describing individual circumstances where extremely high vitamin D doses have been claimed (ranging from 1,250 to 3,750 µg/day vitamin D_2 or D_3), verified by correspondingly high serum 25(OH)D values (ranging from 107 to 1,126 nmol/L), but serum calcium levels were reported to be below the threshold for hypercalcemia (2.65 mmol/L) (69, 70, 90).

Risk assessment

Critical Effect

The critical effect (i.e., the adverse effect occurring at the lowest dosage) chosen for this risk assessment is hypercalcemia, which is consistent with that used previously (15, 35). Clinical symptoms of excessive vitamin D intake include pain, conjunctivitis, anorexia, fever, chills, thirst, vomiting and weight loss, all of which result from hypercalcemia (defined as serum calcium > 2.65 mmol/L) and occur only at very high vitamin D intakes.

The Women's Health Initiative (WHI) involved calcium and vitamin D_3 supplementation in nearly 36,000 post-menopausal women who were randomized to either 1,000 mg calcium and 10 µg (400 IU) vitamin D_3 or placebo daily, with an average follow up of 7.0 years (91). With respect to safety, results showed a significant 17% increased risk in renal stone formation in the supplement group (449 cases) vs. the placebo group (381 cases). In view of the vitamin D doses of greater than several hundred micrograms that have been administered experimentally without any hypercalcemia, it seems unlikely that the vitamin D treatment contributed to the excess risk of renal stones. Further, this study has some well documented limitations, including poor compliance and common use of self-selected calcium and vitamin D supplements in the placebo and treatment groups.

Epidemiological data suggest that neither calcium nor vitamin D intake is associated with an increased risk for renal stone formation (92, 93), or that calcium may be inversely related to the risk for renal stones (94), and its restriction is not encouraged (95, 96). Indeed, a recently issued US government commissioned report concluded that the WHI study remains the only randomized trial of calcium and vitamin D supplementation to observe an increase in renal stone risk (97). Therefore, the literature at present does not appear to support the notion that supplemental vitamin D, including doses at and above the NOAEL identified here (250 µg) in individuals consuming the recommended calcium intake, may increase the risk for renal stone formation in generally healthy adults.

Dose-response assessment

No consistent and reproducible hypercalcemia or any other adverse effect from vitamin D has occurred in well-conducted clinical trials at chronic intakes up to 1,250 µg/day (48, 98) and bolus doses up to 7,500 µg (45-47). The limited duration, size and/or lack of other appropriate design characteristics prevent selection of these doses as a NOAEL that would warrant a high level of confidence. The strong design characteristics and absence of adverse effects in the clinical trials at 250 µg per day (49, 98), and the absence of adverse effects at higher as well as lower levels, continue to justify 250 µg (10,000 IU) per day as the NOAEL for the general healthy population.

Uncertainty evaluation

The absence of adverse effects in clinical trials utilizing intakes up to 1,250 µg per day and the lack of adverse effects at lower levels inspires a high level of confidence in the data from the strongly designed clinical trials at 250 µg/day. Also, in the case reports of toxicity, the 25(OH)D levels have been consistently much higher than those related to known daily intakes of 250 µg of oral vitamin D. In a study by Anning et al. (99), 1,925 µg vitamin D_3/day provided to adults resulted in a serum 25(OH)D level of approximately 600 nmol/L and hypercalcemia. This is the only study to date that might serve as the basis for a Lowest Observed Adverse Effect Level (LOAEL). Thus, an intake of 1,925 µg (77,000 IU) per day may be considered an estimate of the vitamin D LOAEL, and this high level provides further confidence in the selection of UF of 1.0 for calculation of the UL from the NOAEL of 250 µg per day.

Derivation of a recommended UL

Recommended UL = NOAEL ÷ UF = 250 µg per day ÷ 1.0 = 250 µg per day for the general healthy population.

Other reviews that have performed risk assessments and derived ULs or similar values of 50 or 25 µg per day:

Hathcock et al. 2007 vitamin D UL = 250 µg ÷ 1.0 UF = 250 µg per day (35)
US FNB vitamin D UL = 60 µg NOAEL ÷ 1.2 UF = 50 µg per day (15).
EC SCF vitamin D UL = 100 µg NOAEL ÷ 2 UF = 50 µg per day (33).
UK EVM vitamin D “guidance level” for food supplements(100) = 25 µg per day (34).

Exposure estimation

Because vitamin D exposure occurs through both diet and synthesis in the skin under UV light stimulation (101), both must be considered in estimating total exposure. Thus, total vitamin D exposure results from several sources: biosynthesis under UV light stimulation, fortified conventional foods, a few unfortified conventional foods, and dietary supplements. All these sources were taken into account in the most recent published risk assessment (35).

Sun exposure

The maximum amount of vitamin D that can be produced in the skin under UV light stimulation results in serum 25(OH)D levels comparable to those resulting from an oral dose of 250 µg, and requires full-body erythemic light exposure (102); the duration and intensity of UV light exposure necessary to produce a useful amount of vitamin D or provoke an erythemic reaction will depend, of course, on skin pigmentation. While low-to-moderate UV light exposure stimulates vitamin D production, prolonged exposure results in a negative feedback loop destroying vitamin D in the skin (103). Hence, there are no known cases of vitamin D toxicity resulting from extreme or unusually prolonged sun exposure. Chronic exposure to sunlight in outdoor workers at the end of the summer season produce serum 25(OH)D levels equivalent to those with an oral intake of 70 – 125 µg per day (104). Given seasonal and latitudinal variations in sun exposure, the social and cultural efforts of sun avoidance, the amount of time spent indoors by the majority of the population, and the off-setting effects in skin synthesis, long-term vitamin D production from sun exposure is unlikely to exceed approximately 125 µg per day in North America and Europe.

Ordinary foods

Unfortified conventional foods in Western diets contain toxicologically insignificant amounts of vitamin D, amounting to a total on the order of 2.5 µg per day for most consumers (15). Common milk fortification provides 10 µg/quart (105). Thus, ordinary dietary sources, even when combined, usually provide vitamin D amounts well below that of even then current FNB UL (50 µg).

Dietary supplements

Many vitamin D-containing dietary supplements for adults are formulated to provide 5 to10 µg per day or less, when used according to label instructions. Consumption of multiple dietary supplements with vitamin D, for example multivitamins and some calcium products, could produce higher intakes. Such intakes can conceivably exceed both the current FNB UL of 50 µg per day and the proposed new UL. Although availability of products with higher doses is increasing, very few contain doses above 1,250 µg per day if consumed according to label instructions.

Risk characterization

In summary, the combination of all dietary sources (unfortified foods, fortified foods, and most dietary supplements) does not contribute to a total exposure anywhere near the recommended UL of 250 µg per day. There is little prospect of exposure of the healthy general population to toxic levels of vitamin D with current or likely levels in fortified foods and properly used dietary supplements. Therefore, total exposure to vitamin D, including subcutaneous production from UV light exposure, is very unlikely to exceed this proposed UL value. Combining this proposed UL with total erythemic sunlight exposure and typical dietary and supplemental sources all at once would still result in a serum 25(OH)D level (approximately 500 nmol/L) that is well below the estimated level associated with hypercalcemia (>600 nmol/L). Indeed, there is a lot of room for increased vitamin D intakes without risk of overdose. Much larger amounts, up to 7,500 µg, have shown no toxicity if restricted to one occasion per four months (106) or daily for a single period of four days (107) or as bolus doses (45, 46).

Conclusions

The well-established potential of oral vitamin D to produce toxicity if intakes are sufficiently excessive has led to cautious formulation of fortified foods and dietary supplements. However, the present review reinforces the conclusions reached from a previously published risk assessment. Clinical trial data continue to demonstrate that vitamin D is not toxic at intakes much higher than previously considered unsafe. This demonstrated safety profile of vitamin D should safely permit increased intakes to achieve additional benefits of this vitamin at higher levels than previously recognized.

Table 1. Published clinical trial safety observations for vitamin D since 2007

Study & Population	Features	Dosage & study design	Duration (days)	Key Observations	NOAEL Considerations
von Restorff et al. 2009 (108) n = 33	Vitamin D deficient elderly adults	7,500 µg bolus dose vitamin D_3 + 500 – 1000 mg/d calcium; uncontrolled	3 mo (90 d)	Significant increase in serum 25(OH) D to 81.4 nmol/L; no change in mean serum calcium (2.28 mmol/L); two patients with mild hypercalcemia (2.69 mmol/L) resolved at 6 mo; urinary calcium not measured	7,500 µg (300,000 IU), but single bolus dose. Not appropriate for use in identifying NOAEL.
Leventis and Kiely 2009 (45) n = 19	Vitamin D insufficient adults	7,500 µg bolus dose vitamin D_3 or D_2; uncontrolled	24 wk (168 d)	Significant increase in serum 25(OH)D to 134.6 nmol/L; no hypercalcemia observed; urinary calcium not measured	7,500 µg (300,000 IU), but single bolus dose. Not appropriate for use in identifying NOAEL.
Romagnoli et al. 2008 (46) n = 32	Elderly women	7,500 µg bolus dose vitamin D_3 or D_2; uncontrolled	60 d	Significant increase in serum 25(OH) D to 152.8 nmol/L; non-significant increase in serum calcium; no hypercalcemia in any subject; urinary calcium not measured	7,500 µg (300,000 IU), but single bolus dose. Not appropriate for use in identifying NOAEL.
Ilahi et al. 2008 (47) n = 30	Healthy adults	2,500 µg vitamin D_3 single bolus dose; randomized, controlled	1 d	Significant increase in serum 25(OH)D to 105 nmol/L; no significant change in serum calcium; no hypercalcemia in any subject; urinary calcium not measured	2,500 µg (100,000 IU), but only single bolus dose. Not appropriate for use in identifying NOAEL.
Thacher et al. 2009 (109) n = 17	Children with nutritional rickets	1,250 µg bolus dose vitamin D_2 or D_3; randomized, uncontrolled	3 d	Significant increase in serum 25(OH) D to 162.5 nmol/L (D_2 or D_3); significant increase in serum calcium to approximately 2.31 mmol/L (D_2 or D_3); no adverse effects reported	1,250 µg (50,000 IU), but bolus dose in a nutritionally deficient population. Not appropriate for use in identifying NOAEL.
Boas et al. 2009 (110) n = 18	Cystic fibrosis patients	1,250 µg/d vitamin D_2; uncontrolled	14 d	Significant increase in serum 25(OH)D to approximately 145.8 nmol/L; serum and urinary calcium not reported; no adverse effects reported	1,250 µg (50,000 IU), but relatively short duration in a diseased population. Not appropriate for use in identifying NOAEL.
Hiremath et al. 2009 (48) n = 22	Multiple sclerosis patients	1,250 µg/d for 10 d, followed by 178 µg/d for 3 mo, vitamin D_2; randomized, controlled	100 d	Significant increase in serum 25(OH) D to 116 nmol/L; serum and urinary calcium not measured; no adverse effects reported	1,250 µg (50,000 IU), but relatively short duration in a diseased population. Not appropriate for use in identifying NOAEL.
Tarcin et al. 2009 (111) n = 23	Vitamin D deficient adults	7,500 µg/mo (250 µg/d) vitamin D_3 given i.m.; randomized, controlled	3 mo (90 d)	Significant increase in serum 25(OH) D 116.9 nmol/L; no significant change in serum calcium (2.4 mmol/L); no adverse effects reported	250 µg (10,000 IU)/d equivalent, but small sample size and vitamin D deficiency at baseline. Not appropriate for use as a NOAEL.
Heaney et al. 2003 (49) n = 67	Healthy men	0, 25, 125, 250 µg/d vitamin D_3; randomized, controlled; dosing during cold months with little sun exposure expected	20 wk (140 d)	Significant dose-dependent increase in serum 25(OH)D (to 220 nmol/L at highest dose); no significant change in serum calcium	250 µg (10,000 IU) per day in healthy men - NOAEL for this group. Confidence gained by data at 1,250 µg, and 450 µg. Size and duration sufficient. Selected as NOAEL.

Table 1. Continued

Study & Population	Features	Dosage & study design	Duration (days)	Key Observations	NOAEL Considerations
Tucci 2009 (50) n = 56	Adult primary hyperpara-thyroidism patients	1,250 µg/wk (178 µg/d) vitamin D_3; uncontrolled	8 wk (56 d)	Significant increase in serum 25(OH) D to 89.4 nmol/L; no significant change in serum calcium (mean 2.73 mmol/L); 2 patients in whom serum calcium rose from 2.8 to 3.03 mmol/L and 2.83 to 3.05 mmol/L, respectively	178 µg (7,000 IU) does not contradict NOAEL selected above.
Chandra et al. 2008 (51) n = 20	Chronic kidney disease patients	1,250 µg/wk (178 µg/d) vitamin D_3; randomized, controlled	12 wk (84 d)	Significant increase in serum 25(OH)D to 123.5 nmol/L; no significant change in serum calcium; no hypercalcemia in any patient; urinary calcium not measured	178 µg (7,000 IU) does not contradict NOAEL selected above.
Blair et al. 2008 (52) n = 318	Chronic kidney disease patients	1,250 µg/wk (178 µg/d) vitamin D_2; uncontrolled	24 wk (168 d)	Significant increase in serum 25(OH)D to 105 nmol/L; significant decrease in serum calcium; no hypercalcemia in any patient; urinary calcium not measured	178 µg (7,000 IU) does not contradict NOAEL selected above.
Khan et al. 2009 (112) n = 51	Female breast cancer patients	15 or 178 µg/d vitamin D_3 + letrozole; uncontrolled	12 wk (84 d)	Significant increase in serum 25(OH) to 165 nmol/L (median); no hypercalcemia observed	178 µg (7,000 IU) does not contradict NOAEL selected above.
Aloia et al. 2008 (53) n = 138	Healthy adults	Up to 170 µg/d (mean 86 µg) vitamin D_3; randomized, controlled	6 mo (168 d)	Significant increase in serum 25(OHD) to between 75 and 220 nmol/L; no hypercalcemia; 4 subjects experienced hypercalciuria	170 µg (6,800 IU) does not contradict NOAEL selected above.
Wagner et al. 2006 (54) n = 19	Lactating women	160 µg/d vitamin D_3; randomized, controlled	6 mo (168 d)	Significant increase in serum 25(OH) D to 147 nmol/L; no significant change in serum calcium or urinary calcium: creatinine ratio for either mothers or infants	160 µg (6,400 IU) does not contradict NOAEL selected above.
Sneve et al. 2008 (55) n = 445	Overweight and obese adults	2,800 or 5,700 µg/ wk (71 or 143 µg/d, respectively) + 500 mg/d calcium; randomized, controlled	12 mo (365 d)	Significant increase in serum 25(OH) D to 120 nmol/L; no significant change in serum calcium; significant increase in urinary calcium	143 µg (5,700 IU) does not contradict NOAEL selected above.
Mocanu et al. 2009 (56) n = 45	Nursing home residents	125 µg/d vitamin D_3; uncontrolled	12 mo (365 d)	Significant increase in serum 25(OH) D to 125.6 nmol/L; no significant change in serum calcium; no cases of hypercalcemia or hypercalciuria	125 µg (5,000 IU does not contradict NOAEL selected above.
Goldner et al. 2009 (57) n = 45	Gastric bypass patients	20, 50 or 125 µg/d vitamin D_3; randomized, uncontrolled	12 mo (365 d)	Significant increase in serum 25(OH) D to 123.4 nmol/L; no significant change in serum calcium; no cases of hypercalcemia; two cases of hypercalciuria (both in 125 µg/d group)	125 µg (5,000 IU does not contradict NOAEL selected above.
Wagner et al. 2008 (58) n = 80	Healthy adults	100 µg/d vitamin D_3; randomized, controlled	8 wk (56 d)	Significant increase in serum 25(OH)D to approx. 115 nmol/L; small but significant increase in serum calcium vs. placebo, but within normal range; no significant change in urinary calcium	100 µg (4,000 IU) does not contradict NOAEL selected above.

Table 1. Continued

Study & Population	Features	Dosage & study design	Duration (days)	Key Observations	NOAEL Considerations
Fu et al. 2009 (59) n = 98	Healthy adults	100 µg/d vitamin D_3; randomized, controlled (low dose control)	1 yr (365 d)	Significant increase in serum 25(OH)D to 160 nmol/L; no significant increase in serum or urinary calcium	100 µg (4,000 IU) does not contradict NOAEL selected above.
Jean et al. 2009 (113) n = 107	Heamodialysis patients	83 µg/d vitamin D_3; uncontrolled	15 mo (450 d)	Significant increase in serum 25(OH) D to 105.7 nmol/L; no change in serum calcium; urinary calcium not measured	83 µg (3,320 IU) does not contradict the NOAEL selected above.
Zittermann et al. 2009 (60) n = 200	Obese adults	83 µg/d vitamin D_3; randomized, controlled	12 mo (365 d)	Significant increase in serum 25(OH) D to 85.5 nmol/L; no change in serum calcium; urinary calcium not measured	83 µg (3,320 IU) does not contradict the NOAEL selected above.
Tau et al. 2007 (61) n = 18	Healthy children	1,667 µg/mo (approx. 55 µg/d) vitamin D_2; uncontrolled	3 mo (90 d)	Significant increase in serum 25(OH)D to 88.3 nmol/L; serum calcium remained in the normal range; no hypercalcemia observed	Equals 55 µg (2,200 IU) does not contradict the NOAEL selected above.
Maalouf et al. 2008 (62) n = 25 and 340, respectively	Healthy adolescents	350 µg/wk (50 µg/d) vitamin D_3; randomized, controlled	8 wk (56 d), 1 yr (365 d), respectively	Significant increase in serum 25(OH)D up to 95 nmol/L; overall no change in serum calcium, although there were select cases of serum calcium above the normal range (>2.65 mmol/L); urinary calcium not measured	Equals 50 µg (2,000 IU) does not contradict NOAEL selected above.
Hillman et al. 2008 (114) n = 18	Children with arthritis	50 µg vitamin D_3 +/- 1000 mg calcium/d; randomized, controlled (cross-over)	6 mo (180 d)	Significant increase in serum 25(OH)D; no change in serum calcium; no change in urinary calcium	50 µg (2,000 IU) does not contradict NOAEL selected above.
Hillman et al. 2008 (115) n = 15	Children with cystic fibrosis	50 µg vitamin D_3 +/- 1000 mg calcium/d; randomized, controlled (cross-over)	6 mo (180 d)	Significant increase in serum 25(OH) D to 69.1 nmol/L; no change in serum calcium; no change in urinary calcium	50 µg (2,000 IU) does not contradict NOAEL selected above.
Talwar et al. 2007 (63) n = 208	Healthy black women	20 µg/d (2 yr) followed by 50 µg/d (1 yr) vitamin D_3 + 1,200 – 1,500 mg/d calcium; randomized, controlled	3 yrs (1095 d)	Significant increase in serum 25(OH)D to 87 nmol/L; overall no change in serum or urinary calcium, but 6 cases of hypercalcemia and hypercalciuria	50 µg (2,000 IU) does not contradict NOAEL selected above.
Schleithoff et al. 2006 (64) n = 61	Congestive heart failure patients	50 µg vitamin D_3 + 500 mg calcium/d; randomized, controlled	9 mo (270 d)	Significant increase in serum 25(OH)D to 103 nmol/L; no change in serum calcium	50 µg (2,000 IU) does not contradict NOAEL selected above.
Aloia et al. 2005 (65) n = 208	Black post-menopausal women	1200 – 1500 mg/d calcium +/- 20 - 50 µg/d vitamin D_3; randomized, controlled	3 yrs (1095 d)	Significant increase in serum 25(OH)D to 86.9 nmol/L; significant increase in serum calcium in both vitamin D_3 + Ca (to 2.38 mmol/L) and Ca only (to 2.35 mmol/L) groups; significant increase in urinary calcium; all changes observed at 50 µg/d dose	50 µg (2,000 IU) does not contradict NOAEL selected above.
Smith et al. 2009 (66) n = 55	Adults in Antarctica	50 µg vitamin D_3/d; randomized, controlled	5 mo (150 d)	Significant increase in serum 25(OH)D to 71 nmol/L; no change in serum calcium; urinary calcium not measured	50 µg (2,000 IU) does not contradict NOAEL selected above.

Table 2. Vitamin D toxicity case reports – relation to vitamin D_3 dose, serum 25(OH)D, and hypercalcemia

Study & Population	Features	Dosage & study design	Duration	Primary Outcomes
Stephenson and Peiris 2009 (90) n = 1	56-y-old female	3,750 µg/ vitamin D_2/d	28 yrs	No symptoms of vitamin D toxicity; patient was referred as a precaution due to high vitamin D dose used; reported serum 25(OH)D of 107 nmol/L; serum calcium 2.44 mmol/L.
Leu et al. 2008 (68) n = 1	60-y-old female	2,143 µg vitamin D_3/d	10 wk	Reported serum 25(OH)D of 375 nmol/L, accompanied by hypercalcemia (3.8 mmol/L).
Mckiernan and Wiley 2008 (69) n = 2	81 and 75-y-old females	1,250 µg vitamin D_2/d	9 mo	Reported serum 25(OH)D of 602.5 and 500 nmol/L, respectively; serum calcium reportedly normal (2.5 and 2.37 mmol/L, respectively).
Kimball and Vieth 2008 (70) n = 2	56-y-old male; 39-y-old male with MS	200 and 2,200 µg vitamin D_3/d, respectively	Up to 4 years	Reported serum 25(OH)D of 260 and 1,126 nmol/L, respectively; no hypercalcemia or hypercalciuria in 56-y-old; slightly elevated serum calcium (2.63 mmol/L) in 39-y-old.
Taskapan and Vieth 2008 (71) n = 1	77-y-old woman; case report	1,250 µg vitamin D_2/d	> 2 y	Serum 25(OH)D reported to exceed 250 nmol/L, accompanied by hypercalcemia (3.44 mmol/L) and other various toxicity symptoms.
Doneray et al. 2008 (72) n = 2	8-mo-old girl, 25-d-old boy, respectively	30,000 µg (as four bolus doses) and 15,000 µg vitamin D_3 (as one bolus dose)	Unknown	Reported serum 25(OH)D of 525 and 600 nmol/L, respectively, accompanied by hypercalcemia (3.55 and 3.63 mmol/L, respectively) and other various toxicity symptoms.
Tuon et al. 2008 (73) n = 1	38-y-old male HIV patient	17,500 µg vitamin D_3/d	4 mo	Serum 25(OH)D not measured; hypercalcemia (3.85 mmol/L) accompanied by various other toxicity symptoms.
Chatterjee and Speiser 2007 (74) n = 1	16-mo-old boy	Dose unknown; case report	Unknown	Reported peak serum 25(OH)D of 1,680 nmol/L accompanied by hypercalcemia (4.7 mmol/L) and other various toxicity symptoms.
Klontz and Acheson 2007 (75) n = 1	58-y-old woman	4,673 µg vitamin D_3/d	2 mo	Reported peak serum 25(OH)D of 1,171 nmol/L accompanied by hypercalcemia (>3.75 mmol/L) and other various toxicity symptoms.
Orbak et al. 2006 (76) n = 1	7-y-old boy	7,500 µg vitamin D_3/15 d (500 µg/d)	Unknown	25(OH)D not measured; hypercalcemia (3.7 mmol/L) accompanied by various toxicity symptoms.
Drinka et al. 2006 (77) n = 1	89-y-old woman	1,250 µg vitamin D_2/d (combined with 2,000 mg calcium carbonate, then 1,230 mg calcium citrate)	10 d after transition from calcium carbonate to calcium citrate	Reported serum 25(OH)D (after serum calcium returned to normal) of 660 nmol/L, preceded by hypercalcemia (4.2 mmol/L) and accompanied by other various toxicity symptoms.
Chan et al. 2006 (78) n = 1	10-mo-old girl	Dose unknown	Unknown	Reported serum 25(OH)D (after six weeks of follow up) of 174 nmol/L; hypercalcemia (on initial examination; 3.54 mmol/L) and other various toxicity symptoms.

Table 2. Continued

Study & Population	Features	Dosage & study design	Duration	Primary Outcomes
Atabek et al. 2006 (79) n = 1	7-mo-old girl	45,000 µg vitamin D_3/21 d (2143µg/d)	21 d	Reported peak serum 25(OH)D of 881.2 nmol/L accompanied by hypercalcemia (5.2 mmol/L) and other various toxicity symptoms.
Hatun and Cizmecioglu 2005 (80) n = 2	4- and 11-mo-old girls	15,000 µg vitamin D_3 /3 wk (714 µg/d) and 22,500 µg/4 mo (187.5 µg/d), respectively	3 wk and 4 mo, respectively	Reported serum 25(OH)D of 400 – 500 nmol/L accompanied by hypercalcemia (3.7 – 4.5 mmol/L) and other various symptoms of toxicity.
Barrueto et al. 2005 (81) n = 1	2-y-old boy	15,000 µg vitamin D_3/d	4 d	Reported peak serum 25(OH)D of 1,123 nmol/L accompanied by hypercalcemia (3.59 mmol/L) and other various toxicity symptoms.
Vieth et al. 2002 (82) n = 2	29- and 63- y-old males	42,000 µg vitamin D_3/d	7 mo	Reported serum 25(OH)D range of 1,555 – 3,700 nmol/L accompanied by hypercalcemia and other various toxicity symptoms.
Koutkia et al. 2001 (83) n = 1	42-y-old male	3,900 – 65,100 µg vitamin D_3/d	2 yrs	Reported serum 25(OH)D of 1,218 nmol/L accompanied by hypercalcemia and other various toxicity symptoms.
v Muhlendahl 1999 (116) n = 1	7-wk-old infant	5,000 µg vitamin D_3/d;	30 d	Reported serum 25(OH)D of 2,070 nmol/L accompanied by hypercalcemia and other various toxicity symptoms.
Selby et al. 1995 (84) n = 6	Hypervitaminosis D patients	2,500 – 5,000 µg vitamin D_3/d	2 – 13 yrs	Reported serum 25(OH)D range of 533 – 1,203 nmol/L accompanied by hypercalcemia and other various toxicity symptoms.
Pettifor et al. 1995 (85) n = 11	Hypercalcemic patients	50,000 µg vitamin D_3/g cooking oil	10 d	Reported serum 25(OH)D range of 847 – 1,652 nmol/L accompanied by hypercalcemia and other various toxicity symptoms.
Blank et al. 1995 (86) n = 126	Hypervitaminosis D patients	875 – 7,500 µg vitamin D_3/d †; Epidemiologic analysis of industrial mishap	Up to 6 mo	Reported mean serum 25(OH)D of 560 nmol/L in 35 case patients accompanied by various toxicity symptoms.
Jacobus et al. 1992 (87) n = 8	Hypervitaminosis D patients	725 – 4,364 µg vitamin D_3/d†	Up to 6 yr	Reported mean serum 25(OH)D of 731 nmol/L accompanied by hypercalcemia and other various toxicity symptoms.
Jansen et al. 1997 (88) n = 1	85-y-old woman	10 µg vitamin D_3/d	2 mo	Reported serum 25(OH)D of 62 nmol/L accompanied by hypercalcemia (3.31 mmol/L) and other various toxicity symptoms.
Mawer et al. 1985 (89) n = 8	Hypervitaminosis D patients	1,250 – 5,000 µg vitamin D_3/d	Up to 24 yr	Reported serum 25(OH)D range of 583 – 1,843 nmol/L accompanied by hypercalcemia (3.01-4.05 mmol/L) and other various toxicity symptoms.

† Estimated level

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