Risk assessment for vitamin D[1,2]

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ABSTRACT

The objective of this review was to apply the risk assessment methodology used by the Food and Nutrition Board (FNB) to derive a revised safe Tolerable Upper Intake Level (UL) for vitamin D. New data continue to emerge regarding the health benefits of vitamin D beyond its role in bone. The intakes associated with those benefits suggest a need for levels of supplementation, food fortification, or both that are higher than current levels. A prevailing concern exists, however, regarding the potential for toxicity related to excessive vitamin D intakes. The UL established by the FNB for vitamin D (50 μg, or 2000 IU) is not based on current evidence and is viewed by many as being too restrictive, thus curtailing research, commercial development, and optimization of nutritional policy. Human clinical trial data published subsequent to the establishment of the FNB vitamin D UL published in 1997 support a significantly higher UL. We present a risk assessment based on relevant, well-designed human clinical trials of vitamin D. Collectively, the absence of toxicity in trials conducted in healthy adults that used vitamin D dose $\geq$250 μg/d (10 000 IU vitamin D_3) supports the confident selection of this value as the UL. *Am J Clin Nutr* 2007;85:6–18.

KEY WORDS Vitamin D, risk assessment, Tolerable Upper Intake Level, UL

INTRODUCTION

The highest chronic daily oral intake of vitamin D that will pose no risk of adverse effects for most healthy adults has not been elucidated. New clinical research results over the past 10 y indicate that appropriate intakes of vitamin D may provide greater health benefits than previously thought, benefits that include not only improved bone health, but other effects as well. Accumulating epidemiologic and clinical intervention trial data suggest that increased vitamin D status may decrease the risk of cancer, especially that related to colorectal adenomas (1–4). Other evidence suggests that increased vitamin D status may help maintain physical strength in the elderly (5) and also be protective against falls (6). Also, improved vitamin D and calcium status may decrease the prevalence of metabolic syndromes, including diabetes mellitus (7). Treatment with calcium and vitamin D shows some promise for reducing the bone loss in cystic fibrosis patients (8). The health benefits of vitamin D and consequences of inadequacy have been reviewed in detail elsewhere (9, 10). The amounts of vitamin D needed to produce these various beneficial effects ($\geq$20 μg/d equivalent) are greater than that previously thought nutritionally sufficient (5–10 μg/d). The Adequate Intake (AI; 5–15 μg or 200–600 IU vitamin D/d for adults aged $\geq$19 y) identified by the Food and Nutrition Board (FNB) is based on older evidence (11).

Safety is always an important consideration when formulating recommendations for nutrient intake. The FNB evaluated the potential for high intakes of vitamin D to produce adverse effects and set a safe Tolerable Upper Intake Level (UL) of 50 μg (2000 IU) for vitamin D_3 (11). Using similar methodology, the European Commission Scientific Committee on Food (SCF) also identified a vitamin D_3 UL of 50 μg (12). Through a less quantitative application of the same method, the United Kingdom Expert Group on Vitamins and Minerals (EVM) set a vitamin D_3 UL of 25 μg (13).

The FNB selected 60 μg (2400 IU) as the no-observed-adverse-effect level (NOAEL) on the basis of evidence obtained from the clinical trial of Narang et al (14) and selected an uncertainty factor (UF) of 1.2 to calculate the 50 μg UL. In contrast, in their later review, the SCF selected 100 μg from the results of the clinical trial of Vieth et al (15) as the NOAEL and selected a UF of 2 to calculate the 50 μg UL. In a less quantitative approach, the EVM, relying heavily on the data of Vieth et al (15), simply asserted that 25 μg "would not be expected to cause adverse effects in the general population" (12). More recent clinical trial data suggests that the FNB, SCF, and EVM risk assessments are far more restrictive than needed to avoid adverse effects of vitamin D.

Cholecalciferol (vitamin D_3) is produced naturally in human skin exposed to ultraviolet B light (wavelength: 285–320 nm). It occurs in some animal products and is added to various dietary supplements (such as multivitamins) and fortified foods (such as milk). One IU of vitamin D is defined as the activity produced by 0.025 μg cholecalciferol in bioassays with rats (16). Vitamin D_3 is generally considered to be the primary form of dietary vitamin

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D (11), although ergocalciferol (vitamin D_2), a secondary form, is derived from the yeast and plant sterol precursor, ergosterol. Both calciferols appear to be absorbed with equal efficiency, but vitamin D_2 may be less potent (17, 18) and may have a different toxicological profile. The purpose of the present review is to provide a risk assessment for oral vitamin D_3 on the basis of all clinical trials, including data not available at the time the FNB, SCF, and EVM risk assessments were performed.

METHODS

Risk assessments of vitamin D, by using the safe Tolerable Upper Intake Level (UL) method, have been published by the FNB (11), the SCF of the European Commission (12), and the EVM of the United Kingdom (13). The UL method involves three basic, standardized steps: hazard identification, dose-response evaluation, and derivation of the UL (19). *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 relation between oral intake of the nutrient and any adverse effects that result. The 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 (19). The dose-response relation 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 UF selected to describe the uncertainty must reflect these choices within the available data. Whatever NOAEL is identified, the selection of the UL appropriate to those data also can be done aggressively (low UF resulting in a higher UL) or cautiously (high UF resulting in a lower UL). We prefer and use an approach to NOAEL selection that is sufficiently conservative to justify the assignment of a UF of 1.0 in calculation of the UL. Ideally, establishment of a UF of 1.0 warrants selection of a dosage tested in ≥1 adequately designed randomized control trials that is free of adverse effects, is supported by a body of data showing that exposure to much higher doses does not result in toxicity, or both.

Vitamin D differs from typical nutrients in 2 important respects that are pertinent to identification of a NOAEL: *1*) substantial inputs come from endogenous mechanisms (ie, cutaneous synthesis), and *2*) vitamin D possesses a reliable and generally accepted functional status indicator, ie, serum 25-hydroxyvitamin D [25(OH)D]. The latter is helpful not only in assessing adequacy of vitamin D nutriture, but in assessing toxicity as well. In brief, oral inputs that produce steady-state serum 25(OH)D concentrations known not to be associated with toxicity in the population will, ipso facto, be considered to be without adverse effects. We will use this approach to supplement the more usual evaluation of reports of oral dosing studies (ie, the clinical trial evidence).

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 used as the basis of the risk assessment. The clinical trials are considered in order of decreasing daily dosages of vitamin D 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. The clinical trials are listed and briefly described in **Table 1**. The primary criterion for study inclusion was the use of a vitamin D dose substantially above the current AI (≥45 μg or 1800 IU/d), followed by study design (eg, randomized controlled), duration, and sample size. Relevant outcomes include statistically significant changes in serum 25(OH)D and increases in urinary calcium, serum calcium, or both.

Vitamin D_2 and D_3 doses

2500 μg (100 000 IU) vitamin D_3/d

Two trials (20, 21) implemented this dose with the use of 2 different protocols. The trial by Stern et al (20) was well conducted and showed no evidence of adverse effects, but the duration of treatment was only 4 d, a period too short to be useful in assessing possible risk during chronic intake of this vitamin D_3 level. A significant increase in serum 25(OH)D was observed, but no change in serum calcium or phosphorus was seen. The adult cohort included 24 healthy persons who received 2500 μg vitamin D_3/d, but 12 children also were administered the vitamin at a concentration of 37.5 $\mu g \cdot kg^{-1} \cdot d^{-1}$. (The adult dosage provides the same amount per kg body weight as in the children.) These results are supported by the study by Trivedi et al (21) in which 2686 elderly subjects were provided bolus doses of 2500 μg vitamin D_3 once every 4 mo for 5 y (a total of 15 doses). Serum 25(OH)D increased significantly; serum and urinary calcium were not measured, but there were no reports of acute toxicity. Although this study does not equate to a daily dose of 2500 μg, it shows that repeated bolus doses of this magnitude are well tolerated and without adverse effects. Due to the very short duration of the study by Stern et al (20) and to the lack of daily exposure at this dose in Trivedi et al (21), any extrapolation to a NOAEL for long-term daily use would require a substantial UF, but one of uncertain size. Thus, these trials were not selected as the basis for a human NOAEL.

1250 μg (50 000 IU) vitamin D_3/d

In a trial conducted by Barger-Lux et al (22), vitamin D_3 doses of 25, 250, and 1250 μg per day were administered to 38 healthy men for 8 wk during the cold months, a time with limited sun exposure. A significant dose-dependent increase in 25(OH)D was observed up to a concentration of 643 nmol/L. This concentration is generally considered outside the normal range, but serum calcium did not change. The relatively small sample size exposed to this dose ($n = 14$) and the relatively short duration of treatment argue against generalizing from these data for the identification of a UL. Therefore, this trial was not selected as the basis for a human NOAEL because a UF of uncertain size would be required to calculate a UL.

TABLE 1
Published safety observations for vitamin D supplementation[1]

Study	Study population	Dosage and study design	Duration (d)	Key observations	NOAEL considerations
Stern et al 1981 (20)	Healthy adults ($n = 24$) and children ($n = 12$)	Adults: 2500 μg vitamin D_3/d; children: 37.5 $\mu g \cdot kg^{-1} \cdot d^{-1}$, randomized controlled	4 d	Significant increase in serum 25(OH)D; no significant change in serum calcium or phosphorous	2500 μg (100 000 IU), but 4 d only; duration too short for use in assessing chronic intake effects; not appropriate for use in identifying NOAEL
Trivedi et al 2003 (21)	Elderly adults ($n = 2686$)	2500 μg vitamin D_3; randomized controlled[2]	5 y	Significant increase in serum 25(OH)D; serum and urinary calcium not measured; no adverse effects reported	2500 μg (100 000 IU) bolus doses provided once every 4 mo with no acute toxicity reported; long duration (5 y), but not representative of daily exposure at this level; not appropriate for use in identifying NOAEL
Barger-Lux et al 1998 (22)	Healthy men ($n = 38$)	25, 250, and 1250 μg vitamin D_3/d; randomized; dosing during cold months with little sun exposure expected	8 wk (56 d)	Significant dose-dependent increase in serum 25(OH)D (643 nmol/L at highest dose); no significant change in serum calcium	1250 μg (50 000 IU); dosing during cold months may limit extrapolation to long-term safety; appropriate for NOAEL, but with significant uncertainty; supports NOAEL selected below
Kimball et al 2006 (23)	Adult multiple sclerosis patients ($n = 12$)	Progressive increases from 100 to 1000 μg vitamin D_3/d, 1200 mg Ca/d; case study	28 wk (196 d)	Significant increase in serum 25(OH)D (to 385.5 nmol/L); no significant change in serum or urinary calcium	1000 μg (40 000 IU) with 6-wk exposure and no adverse effects, but lack of control group precludes use as NOAEL; supports NOAEL selected below
Hasling et al 1987 (24)	Adults with osteoporosis ($n = 43$)	60 mg NaF/d + 1.9 g Ca/d + 450 μg vitamin D_2/d; case study	5 y (1825 d)	No significant change in serum or urinary calcium at 6–12 mo and 5-y follow-up	450 μg (18 000 IU) for long term, but in adults who may not be representative; high-dose sodium fluoride could confound the effects; NOAEL would have significant uncertainty; supports NOAEL selected below
Rickers et al 1982 (25)	Patients with various diagnoses ($n = 31$)	Prednisone ± 1125 μg vitamin D_2 twice/wk (321 μg/d), 1.4 g Ca/d, 50 mg NaF/d; randomized controlled	6 mo (180 d)	Significant increase in serum 25(OH)D; no significant change in serum calcium	321 μg (12 840 IU), but treatment with prednisone and 4.5 g Ca and high-dose sodium fluoride could confound the outcome; not appropriate for use as NOAEL
Heaney et al 2003 (26)	Healthy men ($n = 67$)	0, 25, 125, and 250 μg vitamin D_3/d; 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 1250 μg and 450 μg; size and duration sufficient; selected as NOAEL
Berlin et al 1986 (27)	Healthy men ($n = 12$)	190 μg vitamin D_3/d; randomized, controlled; dosing during cold months with little sun exposure expected	7 wk (56 d)	Significant increase in serum 25(OH)D to 123 nmol/L; no significant change in serum calcium; significant increase in urinary calcium	190 μg (7600 IU); supports NOAEL selected above
Berlin et al 1987 (28)	Healthy men ($n = 12$)	190 μg vitamin D_3/d followed by calcium load tests (1 g orally); randomized, controlled; dosing during cold months with little sun exposure	7 wk (56 d)	Significant increase in serum 25(OH)D to 123 nmol/L; no significant change in urinary calcium	190 μg (7600 IU); supports NOAEL selected above
Vieth et al 2001 (15)	Healthy adults ($n = 61$)	25 or 100 μg vitamin D_3/d; randomized; dosing during cold months with little sun exposure expected	2–5 mo (60–150 d)	Significant increase in serum 25(OH)D at both doses (96 nmol/L at higher dose); no significant change in serum and urinary calcium	100 μg (4000 IU), safe; supports NOAEL selected above

(*Continued*)

TABLE 1 (*Continued*)

Study	Study population	Dosage and study design	Duration (d)	Key observations	NOAEL considerations
Vieth et al 2004 (29)	Adult thyroid clinic outpatients ($n = 130$)	15 or 100 μg vitamin D_3/d; randomized	≥6 mo (≥180 d)	Significant increase in serum 25(OH)D at both doses (126 nmol/L at higher dose); no significant change in serum calcium	100 μg (4000 IU), safe; supports NOAEL selected above
Hollis et al 2004 (30)	Lactating women ($n = 18$)	Low dose (40 μg vitamin D_2/d + 10 μg vitamin D_3/d) or high dose (90 μg vitamin D_2/d + 10 μg vitamin D_3/d); randomized; subjects instructed to limit sun exposure	3 mo (90 d)	Significant increase in serum 25(OH)D in both high dose (111.3 nmol/L) and low dose (to 90.3 nmol/L) groups; serum calcium reported to have remained in the normal range; no hypercalciuria observed	100 μg (4000 IU) for lactating women, but may not necessarily apply to other adults; supports NOAEL selected above.
Tjellesen et al 1986 (31)	Healthy women ($n = 19$)	100 μg vitamin D_3 or D_2/d + 500 mg Ca/d; randomized; limited sun exposure between mid and late fall	8 wk (56 d)	Significant increase in serum 25(OH)D to 89 nmol/L (D_2) and 113 nmol/L (D_3); significant increase in serum (to 2.51 mmol/L) and urinary calcium in the vitamin D_3 group	100 μg (4000 IU), appears safe but increased urinary calcium; concern about urinary calcium diminished by data at much higher intakes for longer duration in larger cohort; supports NOAEL selected above
Narang et al 1984 (14)	Healthy adults ($n = 30$)	10, 20, 30, 60, or 95 μg vitamin D_3/d; randomized controlled	3 mo (90 d)	Serum 25(OH)D not measured; significant increase in serum calcium (to 2.62 and 2.83 mmol/L) at 2 highest vitamin D_3 doses	95 μg (3800 IU), serum calcium >2.75 nmol/L, considered LOAEL by FNB; not compatible with multiple later studies at higher doses, and with equal or larger cohorts and equal or longer duration; not appropriate for NOAEL or LOAEL
Nordin et al 1985 (32)	Elderly women ($n = 109$)	375 μg vitamin D_2/wk (50 μg/d); randomized controlled	2 y (730 d)	Significant increase in serum 25(OH)D to 59 nmol/L	Equals 53.6 μg (2144 IU), safe; supports NOAEL selected above
Stefikova et al 2004 (33)	Postmenopausal women with osteopenia or osteoporosis ($n = 52$)	500 mg Ca/d ± 375 μg vitamin D_3/wk (50 μg/d); randomized controlled	2 mo (60 d)	Significant increase in serum 25(OH)D to 85 nmol/L; no hypercalcemia (significant decrease in serum calcium to 2.19 mmol/L in control group only); one mild case of hypercalciuria	Equals 53.6 μg (2144 IU), safe; supports NOAEL selected above
Schleithoff et al 2006 (34)	Congestive heart failure patients ($n = 61$)	50 μg vitamin D_3 + 500 mg Ca/d; randomized controlled	9 mo (250 d)	Significant increase in serum 25(OH)D to 103 nmol/L; no change in serum calcium	50 μg (2000 IU), safe; supports NOAEL selected above
Aloia et al 2005 (35)	Black postmenopausal women ($n = 208$)	1200–1500 mg Ca/d ± 20–50 μg vitamin D_3/d	3 y (1095 d)	Significant increase in serum 25(OH)D (86.9 nmol/L); significant increase in serum calcium in both vitamin D_3 + calcium (to 2.38 mmol/L) and calcium only (to 2.35 mmol/L) groups; significant increase in urinary calcium; all changes observed at 50 μg/d dose	50 μg (2000 IU), safe; supports NOAEL selected above
Himmelstein et al 1990 (36)	Elderly nursing home residents ($n = 30$)	50 μg vitamin D_3/d; randomized controlled	6 wk (42 d)	Significant increase in serum 25(OH)D to 80 nmol/L; no significant change in serum calcium	50 μg (2000 IU), safe; supports NOAEL selected above
Johnson et al 1980 (37)	Free-living elderly ($n = 190$)	50 μg vitamin D_3/d (parenterally); randomized controlled	6 mo (180 d)	Serum 25(OH)D not measured; no significant change in mean serum calcium; 2 documented cases of hypercalcemia (>2.65 mmol/L) in treatment group	50 μg (2000 IU), safe; safety at this parenteral dose suggests a much larger oral dose would be safe; supports NOAEL selected above

(*Continued*)

TABLE 1 (*Continued*)

Study	Study population	Dosage and study design	Duration (d)	Key observations	NOAEL considerations
Honkanen et al 1990 (38)	Free-living and institutionalized elderly women (n = 139)	1.5 g Ca/d + 45 μg vitamin D_3/d; randomized controlled; dosing during cold months with little sun exposure expected	11 wk (77 d)	Significant increase in serum 25(OH)D to 81 nmol/L; significant increase in serum calcium (to 2.73 mmol/L) in the institutionalized control group only	45 μg (1800 IU), safe; supports NOAEL selected above

[1] NOAEL, no-observed-adverse-effect level; LOAEL, lowest-observed-adverse-effect level; FNB, Food and Nutrition Board; 25(OH) D, serum 25-hydroxyvitamin D. 1 μg = 40 international units (IU). Normocalcemic range = 2.15–2.65 mmol/L.The primary criterion for study inclusion was vitamin D dose, with inclusion of studies involving ≥45 μg (1800 IU)/d, followed by study design (eg, randomized controlled), duration, and sample size.

[2] Representative of single bolus doses provided once every 4 mo for 5 y (15 in total).

450 μg (18 000 IU) vitamin D_2/d

The trial by Hasling et al (24) was very long-term (5 y), involved a substantial cohort (43 osteoporosis patients), and there was no evidence of adverse effects of vitamin D. Nonetheless, these data do not support a general NOAEL for chronic use because the subjects were also given high doses of sodium fluoride at 60 mg/d (27 mg fluoride) and of calcium phosphate at 6 g/d (1.9 g calcium). Also, rather than vitamin D_3, this trial used vitamin D_2, which is metabolized and cleared from the body more rapidly than the animal form of the vitamin (18). Although the absence of hypercalcemia or hypercalciuria in these subjects despite relatively high doses of vitamin D_2 and calcium is reassuring, these data were not selected as the basis for a general use NOAEL for vitamin D because of the potential for confounding and the uncertainty involved in an extrapolation from this population to the general population of healthy adults.

321 μg (12 840 IU) vitamin D_2/d

Rickers et al (25) conducted a trial in which a 321 μg vitamin D_2/d average dose given for 6 mo was administered as 1125 μg vitamin D_2 twice/wk to 31 patients with various diagnosed illnesses. No obvious adverse effects of vitamin D were observed, but the results were potentially confounded by prednisone treatment and high doses of sodium fluoride at 50 mg/d (22 mg fluoride) and calcium phosphate at 4.5 g/d (1.4 g calcium). The absence of hypercalcemia despite the high dose of calcium is reassuring. Nevertheless, the diseased conditions of the subjects, the use of vitamin D_2, and confounding by prednisone and fluoride increase the uncertainty and decrease the confidence in extrapolation of the data to identify a NOAEL for general chronic use of vitamin D.

250 μg (10 000 IU) vitamin D_3/d

Two well-conducted clinical trials by Heaney et al (26) and Barger-Lux et al (22) involved cohorts of healthy men divided into groups and administered increasing doses of vitamin D_3 for 8 and 20 wk, respectively. Both studies were conducted during the cold months at a latitude of >40 °N, thus limiting the subjects' sun exposure. In the 2 studies, serum 25(OH)D increased significantly up to mean values of 213 nmol/L (n = 10) and 220 nmol/L (n = 16), respectively, which are values comparable to those achieved with whole-body UV light exposure (39, 40). Serum calcium was not increased and no significant adverse effects occurred in either study, indicating that this vitamin D_3 intake was safe for this combined cohort of 26 healthy men and for this duration. In Heaney et al (26), a separate group of subjects (n = 15) who received 125 μg vitamin D_3/d also experienced a significant increase in serum 25(OH)D (to 160 nmol/L) with no change in serum calcium. Although the subjects in these clinical trials were healthy men and possibly more resistant to the potential adverse effects of vitamin D than are other population groups, some of the clinical trials that used higher intakes also included men and women with various disease conditions and cotreatments (eg, high-dose calcium supplementation), which may have made them more susceptible to excess vitamin D. Combining the results of these 2 well-conducted studies with the absence of toxicity in normal subjects exposed to a 5-fold dose [1250 μg vitamin D_3/d (22)] warrants a high level of confidence in the selection of 250 μg/d as the NOAEL for vitamin D_3.

190 μg (7600 IU) vitamin D_3/d

These studies conducted by Berlin et al (27, 28) were a series of two 7-wk clinical trials involving 12 healthy men. The 190 μg vitamin D3/d dose used in both trials produced significant increases in serum 25(OH)D (to 123 nmol/L). In the Berlin et al study conducted in 1986 (27), there was no significant change in serum calcium, whereas urinary calcium did increase significantly. In the Berlin et al study conducted in 1987 (28), a calcium loading test (equivalent to 1 g elemental calcium orally) was added to the protocol. Results showed no effect on urinary calcium. No adverse effects were observed in either trial.

100 μg (4000 IU) vitamin D_2 or D_3/d

These 4 clinical trials [Vieth et al (15, 29); Hollis et al (30); and Tjellesen et al (31)] involved 100 μg vitamin D/d, but in one the intake consisted of 90 μg vitamin D_2 and 10 μg vitamin D_3. The treatment periods ranged from 56 d to 14 mo, and the cohort sizes were from 18 to 130. The subjects included healthy adults, adult thyroid clinic outpatients, lactating women, and healthy nonlactating women. All studies produced increases in 25(OH)D above baseline that remained well within the range commonly observed in outdoor workers during the summer months, and none resulted in any adverse effects (41–43).

95 μg (3800 IU) vitamin D_3/d

This clinical trial, conducted by Narang et al (14), involved 30 healthy adults divided among treatment doses of 10, 20, 30, 60, and 95 μg vitamin D_3/d. No adverse clinical effects were reported, but the highest intake produced a significant increase in serum calcium to 2.83 mmol/L, a concentration slightly above

the reported upper normal level of 2.75 mmol/L. Serum 25(OH)D was not measured. These results are very different from those in later studies that used higher doses given to larger cohorts and for longer durations. Thus, these results are inconsistent and conflict with the preponderance of the clinical trial database for high-dose vitamin D and therefore are not considered to credibly contradict the 250 μg NOAEL.

53.6 μg (2144 IU) vitamin D_3/d average based on a weekly dose of 375 μg (150 000 IU) vitamin D_3

This 2-y study by Nordin et al (32) conducted in 109 elderly women produced significant increases in 25(OH)D but no adverse effects.

Possible NOAEL selection from clinical effects and serum 25(OH)D

The serum 25(OH)D concentration is accepted as the most appropriate indicator of vitamin D status (11). Selection of a NOAEL for vitamin D is aided by consideration of how serum 25(OH)D concentrations relate to toxicity. More specifically, given the multiple sources of vitamin D (cutaneous biosynthesis, foods, and supplements), the serum 25(OH)D concentrations at which hypercalcemia occurs must be examined to ascertain how overall status relates to toxicity (ie, the critical dose-response relation). A comprehensive review of the literature revealed that the serum 25(OH)D concentrations associated with hypercalcemia were almost exclusively the result of very large doses of vitamin D, and in all instances serum 25(OH)D concentrations reached concentrations well into the hundreds and even thousands of nmol/L (44). This is consistent with the data derived by Mason et al (45) and reported recently by Morris (46), which concluded that, on the basis of the relation between the 2 parameters, a serum 25(OH)D concentration of ≥700 nmol/L may be needed to evoke hypercalcemia in normal adults.

On the basis of the data from Heaney et al (26), which showed no change in serum calcium associated with a serum 25(OH)D concentration of 220 nmol/L at an oral intake of 250 μg vitamin D_3/d, 220 nmol/L is selected as the serum 25(OH)D concentration that occurs at the intake selected as the healthy adult NOAEL. This choice is justified by the absence of adverse effects in the subjects who consumed this amount, and confidence is also increased by the absence of adverse effects in subjects who were administered much larger doses, up to 2500 μg, in which the achieved 25(OH)D concentrations were up to several-fold the 220 nmol/L observed by Heaney et al (18, 20–22). Similarly, there were no adverse effects in most clinical trials that used lower doses (41–43). The possible adverse effect of increased serum calcium with an oral dose of 95 μg vitamin D/d (14) is inconsistent with the totality of the evidence, suggesting that some mistake, perhaps in the identification or administration of the vitamin D dose, may have occurred. Furthermore, the absence of serum 25(OH)D measurement in this study makes it impossible to validate the reported vitamin D doses. Certainly, there is no confirmation for that observation by other studies, even with much higher vitamin D intakes.

A report by Rizzoli et al (47) of serum 25(OH)D concentrations in 7 cases of apparent vitamin D intoxication does not clarify the dose-response relation between vitamin D and this metabolite. This was a single series of case reports in which there was no consistent relation between dosage and serum 25(OH)D, a fact which sheds doubt on either the vitamin D intake or the serum 25(OH)D assay, and for that reason we have chosen not to give credence to its values.

ADVERSE EFFECTS REPORTS

There are numerous reports of accidental or uninformed consumption of very high doses of vitamin D (11, 48–57) (**Table 2**). The data convincingly support causality only in the cases with exposure levels far above those administered in the clinical trials discussed above. A few cases illustrate the point. Mistaken administration of 2.4 million IU vitamin D over a 4-d period (15 000 μg/d) to a 2-y-old boy produced resistant hypercalcemia and hypertension (49). An isolated incident of accidental or intentional mixing of crystalline vitamin D_3 into the table sugar of one family resulted in vitamin D intakes as high as 42 000 μg/d for several months (50). The toxic signs of the resulting hypercalcemia included pain, conjunctivitis, anorexia, fever, chills, thirst, vomiting, and weight loss. A 72-y-old man with a 10-d history of nausea, vomiting, and weight loss subsequent to a month of thirst, polyuria, and poor mental concentration was found to have consumed 15 000 μg vitamin D_2/d for 21 d (48). These reports provide recent examples that confirm the acute toxic potential of elevated serum calcium concentrations caused by extraordinary intakes of vitamin D, an effect first established decades before.

Some reports related to doses lower than the foregoing, but most were still above our NOAEL and seemed always to have involved patients with compromised health or other confounding factors. Four cases in a single report illustrate this phenomenon (58): a 77-y-old woman with severe osteoporosis had a vitamin D intake of 1250 μg/d and hypercalcemia; a 42-y-old woman with nephritic syndrome, hypertension, and renal insufficiency being treated with hydrochlorothiazide developed hypercalcemia while taking 1250 μg vitamin D_2/wk; a 68-y-old woman who had a history of hypertension treated with hydrochlorothiazide and α-methyldopa developed hypercalcemia while being treated with prednisone and taking 1250 μg vitamin D/d; and a 76-y-old woman taking prednisone for many years for bronchospasm developed hypercalcemia while taking 1250 μg vitamin D_2 twice per week. (In the second and fourth cases, the vitamin form was specified as D_2; in the first and third, the type was unspecified, but is considered likely to have been D_2 as well.)

Of the reported cases of vitamin D toxicity, nearly all have involved doses higher than those used in the clinical trials reviewed (Table 2); patients with compromised health, especially renal insufficiency; or confounding by hydrochlorothiazide treatment (*see* below) or other factors. The 25(OH)D concentrations reported were consistently higher than those seen with a vitamin D_3 daily dose of 250 μg. Thus, the case reports are not appropriate or useful as the basis of a NOAEL for the general population. In contrast, the cases exhibiting toxicity all had serum 25(OH)D concentrations ranging from 700 to >1600 nmol/L (49, 50, 53, 55). This fact increases the confidence in the NOAEL of 250 μg, because the 25(OH)D concentrations typically achieved with that intake (220 nmol/L) (26) are much lower. There is one published case report of an 85-y-old woman experiencing hypercalcemia and other adverse effects from a relatively low dose of vitamin D_3 (10 μg/d for 2 mo) (56). The serum 25(OH)D concentrations on admission were 62 nmol/L, well below that believed to be associated with toxicity. This appears to be an aberrant case that has not been replicated elsewhere in the literature.

TABLE 2
Vitamin D toxicity—relation to vitamin D_3 dose, serum 25-hydroxyvitamin D_3 [25(OH)D_3], and hypercalcemia

Study	Study population	Dosage and study design	Duration	Primary outcomes
Barrueto et al 2005 (49)	2-y-old boy (n = 1)	15 000 μg vitamin D_3/d; case report	4 d	Reported peak serum 25(OH)D_3 of 1123 nmol/L accompanied by hypercalcemia (7.2 mmol/L) and other various toxicity symptoms
Vieth et al 2002 (50)	29- and 63-y-old men (n = 2)	42 000 μg vitamin D_3/d; case report	7 mo	Reported serum 25(OH)D_3 range of 1555–3700 nmol/L accompanied by hypercalcemia and other various toxicity symptoms
Koutkia et al 2001 (51)	42-y-old man (n = 1)	3900–65 100 μg vitamin D_3/d; case report[1]	2 y	Reported serum 25(OH)D_3 of 1218 nmol/L accompanied by hypercalcemia and other various toxicity symptoms
Selby et al 1995 (52)	Hypervitaminosis D patients (n = 6)	2500–5000 μg vitamin D_3/d; case report	2–13 y	Reported serum 25(OH)D_3 range of 533–1203 nmol/L accompanied by hypercalcemia and other various toxicity symptoms
Pettifor et al 1995 (53)	Hypercalcemic patients (n = 11)	50 000 μg vitamin D_3/g cooking oil; case report	10 d	Reported serum 25(OH)D_3 range of 847–1652 nmol/L accompanied by hypercalcemia and other various toxicity symptoms
Blank et al 1995 (54)	Hypervitaminosis D patients (n = 126)	875–7500 μg vitamin D_3/d; epidemiologic analysis of industrial mishap	≤6 mo	Reported mean serum 25(OH)D_3 of 560 nmol/L in 35 case patients accompanied by various toxicity symptoms
Jacobus et al 1992 (55)	Hypervitaminosis D patients (n = 8)	725–4364 μg vitamin D_3/d; case report[1]	Up to 6 y	Reported mean serum 25(OH)D_3 of 731 nmol/L accompanied by hypercalcemia and other various toxicity symptoms
Jansen et al 1997 (56)	85-y-old woman (n = 1)	10 μg vitamin D_3/d; case report	2 mo	Reported serum 25(OH)D_3 of 62 nmol/L accompanied by hypercalcemia (3.31 mmol/L) and other various toxicity symptoms
Mawer et al 1985 (57)	Hypervitaminosis D patients (n = 8)	1250–5000 μg vitamin D_3/d; case report	Up to 24 y	Reported serum 25(OH)D_3 range of 583–1843 nmol/L accompanied by hypercalcemia (3.01–4.05 mmol/L) and other various toxicity symptoms

[1] Estimated doses.

RISK ASSESSMENT

Critical effect

The potential for high serum calcium to produce adverse physiologic effects warrants selection of this endpoint as the critical effect, ie, the adverse effect occurring at the lowest dosage, a selection consistent with that of the FNB in 1997. Excessive vitamin D intake is associated with additional significant clinical adverse effects, including pain, conjunctivitis, anorexia, fever, chills, thirst, vomiting, and weight loss. These are all due to hypercalcemia and occur only at very high vitamin D intakes. By themselves, these symptoms do not qualify as the critical effect in a risk assessment (59). Hypercalciuria (defined as 24-h calcium-to-creatinine molar ratios >1) may be a more sensitive indicator of vitamin D adverse effects than is hypercalcemia. However, this ratio may change for reasons other than calcium or vitamin D effects; eg, changes or differences in urinary creatinine unrelated to calcium metabolism will alter this ratio.

The recently published Women's Health Initiative (WHI) involving calcium and vitamin D_3 supplementation has raised concerns about the potential for this combination to increase the risk of renal stones (60). The study involved nearly 36 000 postmenopausal women who were randomly assigned to receive either 1000 mg calcium and 10 μg (400 IU) vitamin D_3/d or placebo, with an average follow up of 7 y. With respect to safety, results showed a significant 17% increased risk of renal stone formation in the supplement group (449 cases) compared with the placebo group (381 cases). The high use of self-selected supplements indicates that calcium intake in the experimental group was upwards of 2000 mg. In view of the vitamin D supplement levels of 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.

Although an increased relative risk of renal stones was observed in the Nurses' Health Study (61) for those supplementing with any amount of calcium [multivariate relative risk: 1.20 (95% CI: 1.02, 1.41)], the data gave no support for a dose-response effect (relative risk: 1.26 for 1–100 mg supplemental calcium/d compared with 1.21 for ≥501 mg/d). The lack of a dose-response pattern suggests that a causal relation to the supplemental calcium is unlikely. Moreover, these findings relate to calcium and do not imply that vitamin D would have the same effect.

According to Heaney et al (26), the 10 μg vitamin D_3 dose used in the WHI study increased serum 25(OH)D by ≈7 nmol/L, an amount far below that believed to produce hypercalcemia, which is the antecedent to hypercalciuria. This increase above the relatively low baseline serum 25(OH)D concentration in the WHI study would be expected to have produced final concentrations far below those observed in association with hypercalcemia. Thus, the inconsistency and lack of a dose-response relation in the entire published database argue that the renal stone occurrence in the WHI study is unlikely to be causally related to the vitamin D supplement. 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. The WHI study reported a significant (29%) reduction in hip fracture risk among those women who adhered to the supplement regimen. Whether the risk of renal stones was further increased in these more treatment-compliant women is unknown, because this was not addressed in the article.

Numerous randomized controlled trials have been conducted with the use of comparable doses of calcium, vitamin D_3 supplementation, or both, albeit with smaller sample sizes and shorter durations than those used in WHI; however, none have reported an increase in the incidence of renal stones in the case group compared with the placebo group. Several studies have reported on the effects of combining a relatively high oral dose of vitamin D_3 (≥50 μg or 2000 IU/d) and calcium (≥500 mg/d). Although a few have reported significant increases in urinary calcium (31, 35), most have not (23–25, 28, 34) (Table 1). The heterogeneity in the respective study designs precludes drawing any firm conclusions, but the effect on urinary calcium does not appear to be related to either the vitamin D_3 or calcium dose. Kimball et al (23) recently showed that combining up to 1000 μg (40 000 IU) vitamin D_3 with 1200 mg calcium/d resulted in no significant increase in serum or urinary calcium in a group of multiple sclerosis patients. Epidemiologic data suggest that neither calcium nor vitamin D intakes are associated with an increased risk of stone formation (62, 63) and that calcium intakes may be inversely related to the risk of renal stones (64); therefore, calcium intake restriction is not encouraged (65, 66). Thus, 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 persons consuming the recommended calcium intake, may increase the risk of renal stone formation in generally healthy adults. However, the absence of prospective, dose-ranging studies in those who may be more sensitive to the effects of vitamin D and supplemental calcium (ie, stone formers) suggests that this effect cannot be categorically ruled out. The need remains for a prospective study of the effects of incremental increases in vitamin D and supplemental calcium on urinary calcium excretion in stone formers and non–stone formers.

Cardiovascular disease is known to be a major cause of mortality in dialysis patients (67) and is believed to be related primarily to vascular calcification (68). In these patients, phosphate absorption is normal but renal excretion is severely impaired, resulting in hyperphosphatemia, which appears to be the cause of soft tissue calcification. Vitamin D status is low in most patients with end-stage renal disease, and there is no evidence that vitamin D contributes to the calcification in the cardiovascular pathology of end-stage renal disease. In fact, treatments include administration of 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], its analogues, or both along with phosphate binders (69). Although vitamin D_3 was implicated as a potential cause of soft tissue calcification (70), this assertion is not supported by the available human data.

Some animal studies have used 1,25$(OH)_2D_3$ or related analogues to induce hypercalcemia and cause calcification (70–73), with some reports having confused or misused terminology by equating vitamin D_3 with the active hormone (70, 72). This latter point was recently illustrated in a Letter to the Editor (74) in which the responding researchers (Norman and Powell), acknowledged that in their 2005 review (70), "...We never stated or contended that vitamin D nutrition causes peripheral arterial disease..." and that "...we used the term 'vitamin D' generically on some occasions and agree this lack of precision sometimes can cause ambiguity...".

Other animal studies have involved extraordinarily high doses of vitamin D_3, achieving serum 25(OH)D concentrations on the order of 2000 nmol/L, with conflicting results (75–78). Toda et al (76) appear to have administered high doses of vitamin D_3 to pigs (100 000 to 4 000 000 IU per ton of ration) for up to 4 mo and reported no significant differences in serum calcium and several other variables (serum cholesterol, triacylglycerols, and phospholipids) between the various treatment groups, but with dose-responsive intimal thickening. Given the lack of effect on these serum variables, the authors postulated that vitamin D_3 was having a direct effect as an "angiotoxin." Although serum 25(OH)D concentrations were mentioned to have been comparable to those of the American population, no data are provided, thus limiting the confidence in the conclusions of this publication. The finding of no increase in serum calcium observed by Toda et al (76) is in contrast with more recent, more rigorously designed animal trials. Montgomery et al (77, 79) provided bolus doses of between 500 000 and 7 500 000 IU vitamin D_3/d for 9 d to cattle, which resulted in serum 25(OH)D concentrations of up to 1500 nmol/L accompanied by hypercalcemia. In a more recent study, researchers provided 40 000 or 80 000 IU vitamin D_3/kg of feed to pigs for 7 wk, achieving serum 25(OH)D concentrations of 810 and 1936 nmol/L, respectively (78). Only the group receiving the 80 000 IU dose experienced a significant increase in serum calcium, a finding consistent with human data suggesting serum 25(OH)D concentrations >600 nmol/L are required to elicit hypercalcemia in normal adults (46, 80). Collectively, these data illustrate 2 key points: *1*) in animal models, as would be expected, extraordinarily high doses of vitamin D_3 or direct administration of 1,25$(OH)_2D_3$ (and related analogues) at high doses result in sizeable elevations in both serum 25(OH)D and calcium; and *2*) it is the resulting hypercalcemia, not vitamin D_3, that is most likely responsible for the few observations of arterial calcification. The data from Toda et al (76) are likely to be an aberration, because studies repeating these apparently high vitamin D_3 doses have observed large increases in serum 25(OH)D along with elevated serum calcium. Furthermore, the serum 25(OH)D concentrations achieved in these studies (approaching and exceeding 1000 nmol/L) are up to 5-fold those achieved by the NOAEL suggested here (220 nmol/L). Therefore, the risk of soft tissue calcification in humans can be considered more an artifact of the active hormone than of vitamin D_3 itself, and there is likely no risk at the NOAEL chosen.

Dose-response assessment

No consistent and reproducible hypercalcemia or any other adverse effect from vitamin D has occurred in well-conducted clinical trials at intakes up to 1250 μg/d. The limited duration, size, or lack of other appropriate design characteristics prevent the selection of intakes of 1250, 450, or 321 μg vitamin D/d 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 vitamin D/d (22, 26) and the absence of adverse effects at higher as well as lower doses justify the selection of 250 μg (10 000 IU) vitamin D/d as the NOAEL for the general healthy population.

The report of Barger-Lux et al (22) stated there was no significant change in circulating calcium concentration; we have since retrieved the total serum calcium values from that study. In the 14 men receiving 1250 μg vitamin D_3/d, mean ($\pm$SD) initial serum calcium was 9.58 $\pm$ 0.29 mg/dL, and after 8 wk of supplementation it was 9.70 $\pm$ 0.19 mg/dL, for which the 2-tailed paired *t* test showed no significant difference (P = 0.18). These data might support 1250 μg vitamin D_3/d as the NOAEL, but given the relatively short term of the study and the healthy male cohort that may not extrapolate well to the general population, selection of this value as the NOAEL would require the application of a UF >1.0 in calculation of the UL. Thus, our selection of a NOAEL of 250 μg vitamin D/d as the basis of the UL is well justified.

Sensitive subpopulations

Persons with certain health conditions, notably sarcoidosis and *Mycobacterium* infections, and those treated with thiazide diuretics are reported to be extremely sensitive to excessive vitamin D (11, 81–84). Although there is an absence of recent human intervention trials examining the effect of vitamin D treatment in persons with sarcoidosis or a *Mycobacterium* infection, data exist in the literature suggesting that these persons may not be as vitamin D–sensitive as many believe. Anning et al (80) conducted a 21-mo trial in a group of 200 patients with underlying diseases, including lupus vulgaris, tuberculosis, and sarcoidosis, and found that a vitamin D_3 doseof >1100 IU $\cdot$ kg^{-1} $\cdot$ d^{-1} (equivalent to 77 000 IU or 1925 μg in a 70-kg man) was required to cause hypercalcemia in this cohort. Although this study does not provide a basis for a NOAEL for this subpopulation, the results suggest that a NOAEL of 250 μg would be well tolerated and not result in adverse effects in persons with these diseases.

Only 2 relevant human studies address vitamin D in combination with thiazides. In one, the cotreatment of rachitic children with $1,25(OH)_2D_3$ at a dose of 58 ng $\cdot$ kg^{-1} $\cdot$ d^{-1}, together with 0.8 mg $\cdot$ kg^{-1} $\cdot$ d^{-1} hydrochlorothiazide, for 3 y resulted in no changes in serum calcium (85). In another small case study, 2 patients who were cotreated with a thiazide diuretic and 2.5 mg (100 000 IU) vitamin D_2 or D_3, respectively, for 7 d experienced hypercalcemia (86). The above cited cases involved administration of either the active form of vitamin D, $1,25(OH)_2D_3$ (85), which bypasses usual physiologic control systems, or a much larger (2.5 mg) dose of vitamin D (86), neither of which casts doubt on the chosen NOAEL of 250 μg.

In analyzing the relation between thiazides and vitamin D, Arfitt (86) concluded that thiazides are likely to be a risk factor for hypercalcemia only in situations in which there is uncontrolled entry of calcium into the extracellular fluid, as, for example, in cases of multiple myeloma (81). Heaney et al (43) showed that calcium absorptive input from the gut is maximized at a serum 25(OH)D concentration of 80 nmol/L and does not rise as 25(OH)D continues to increase out to at least 200 nmol/L. For this reason, as well as because there is no other evidence to suggest that the selected NOAEL would produce excessive calcium inputs from bone or gut into the extracellular fluid, we conclude that, although direct experimental evidence of the safety of the NOAEL in thiazide users is not available, it is unlikely that thiazides, per se, would significantly alter sensitivity to a vitamin D intake in the range of the NOAEL.

Uncertainty evaluation

The absence of adverse effects in clinical trials that used intakes up to 1250 μg vitamin D/d and the lack of adverse effects at lower doses inspires a high level of confidence in the data from the strongly designed clinical trials that used 250 μg vitamin D/d. Also, the 25(OH)D concentrations in the case reports of toxicity were almost always much higher than those that used 250 μg oral vitamin D intake. In situations in which adequate data showing a NOAEL are lacking, a LOAEL, the lowest intake or experimental dose at which an adverse effect has been identified, could be used as the basis for a UL but would, by definition, require the application of a UF >1.0 in calculation of the UL (19). In this case, where we have identified a NOAEL with considerable confidence, identification of a LOAEL, although not strictly necessary, can nevertheless provide further support for the chosen NOAEL value. At present, the study by Anning et al (80), in which an adult vitamin D_3 dose >1925 μg was needed to elicit hypercalcemia, is the only study that may serve as the basis for a LOAEL. This intake dose is the lowest that is established to lead not only to hypercalcemia, but also to serum 25(OH)D concentrations in the order of 600 nmol/L, which are associated with hypercalcemia. Thus, an intake of 1925 μg (77 000 IU) vitamin D/d may be considered an estimate of the vitamin D LOAEL. Furthermore, the possibly increased vitamin D sensitivity of the patients used in the study suggests that this may be a conservative estimate for normal persons and therefore reduces uncertainty and provides additional assurance for the selected NOAEL. Thus, a UF of 1.0 is selected for calculation of the UL from the NOAEL of 250 μg vitamin D/d.

The identification of a NOAEL is an exercise in the proof of a negative, ie, that no adverse effect occurs, and these always leave some residual uncertainty. This low level of uncertainty does not preclude the selection of a UF of 1.0, as exemplified by the FNB risk assessments on fluoride (11) and manganese (87). Our approach to the identification of a vitamin D NOAEL is to reject higher potential NOAEL values because of the significant uncertainty and to select a NOAEL that justifies a UF of 1.0. We judge the overall database and that specifically on 250 μg vitamin D to justify a UF of 1.0 when this amount is selected as the NOAEL.

Derivation of a recommended UL

The recommended UL = NOAEL/UF = (250 μg vitamin D/d)/1.0 = 250 μg vitamin D/d for the general healthy population. Official reviews have performed risk assessments and de-

rived UL or similar values of 50 or 25 μg per day. The US FNB derived UL as follows (11):

$$\text{US FNB vitamin D UL} = 60\ \mu\text{g NOAEL}/1.2\ \text{UF} = 50\ \mu\text{g/d} \quad (1)$$

The EC SCF derived UL as follows (12):

$$\text{EC SCF vitamin D UL} = 100\ \mu\text{g NOAEL}/2\ \text{UF} = 50\ \mu\text{g/d} \quad (2)$$

and the UK EVM derived the "guidance level" as follows (13):

$$\text{UK EVM vitamin D "guidance level"} = 25\ \mu\text{g/d} \quad (3)$$

The EVM guidance level value was identified through a less formal application of the UL method in which a total vitamin D exposure of 25 μg/d was not derived from the NOAEL-UF procedure but was judged to be a level that would not "cause adverse effects in the general population" (13). This caution seems to relate to an uncritical extrapolation of the results from a parenteral dose of 50 μg vitamin D/d [Johnson et al (37)] to conclusions about oral intake.

Consideration of sex

To establish a UL for any nutrient, optimal data on both men and women would be ideal but often does not exist. In these cases, the FNB has extrapolated from data from one sex to another sex (eg, zinc) to establish a UL (87). In the present review, although the NOAEL has been selected from a trial involving only men (26), several published clinical trials conducted with both men and women at higher doses have observed no sex-specific differences related to safety (21, 23–25). In addition, men tend to have a higher vitamin D status than do women (88–90), and thus administration of a given amount of vitamin D_3 would result in higher serum 25(OH)D concentrations in men than in women. The proposed UL value is therefore likely to be a conservative estimate for women.

It is well established that indexes such as adiposity and body mass index are inversely related to serum 25(OH)D concentrations (91–93). Because women tend to have higher percentage body fat than do men, it follows that at a given vitamin D exposure level, and with control for other confounders, women may have lower serum 25(OH)D concentrations than do men. Although clearly there is a sex-specific difference in vitamin D metabolism, this does not necessarily place women at more or less risk of toxicity, and, in fact, this is not supported by the available literature. In contrast to some assertions, studies conducted on morbidly obese persons who have undergone rapid weight loss (from, for example, bariatric surgery) show no toxic effects from vitamin D released from catabolized adipose tissue and, in fact, often reveal several nutrient deficiencies, including vitamin D (94). Therefore, although no systematic analysis has been conducted to assess sex differences with respect to safety, there is currently no basis to believe there would be a clinically relevant difference.

EXPOSURE ESTIMATION

Because vitamin D exposure occurs through both diet and synthesis in the skin under UV light stimulation (40), 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.

Sun exposure

The maximum amount of vitamin D that is cutaneously produced under UV light stimulation, creating serum 25(OH)D concentrations similar to those resulting from an oral dose of 250 μg, occurs principally at full-body erythemic light exposures (95) and consequently is unlikely to occur frequently. Low and moderate levels of UV light exposure stimulate vitamin D production, but prolonged exposure destroys vitamin D in the skin (96). 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 concentrations equivalent to those with an oral intake of 70–125 μg vitamin D/d (43). Given seasonal and latitudinal variations in sun exposure, the amount of time spent indoors by most of the population, and the off-setting effects in skin synthesis, long-term vitamin D production from sun exposure is unlikely to exceed ≈125 μg/d in North America and Europe.

Ordinary foods

Unfortified conventional foods in Western diets contain nutritionally useful but toxicologically insignificant amounts of vitamin D, amounting to a total on the order of 2.5 μg/d for most consumers (11). Common milk fortification provides 10 μg/quart, a small amount compared with our recommended UL of 250 μg and still small compared with the FNB UL of 50 μg. Accidental dietary intakes from misformulated fortified milk have produced extremely high and toxic exposures, estimated as high as 7500 μg/d (54), but fortunately such occurrences are infrequent. Mistaken use of vitamin D concentrates has occasionally resulted in acute vitamin D intoxication in infants (49). Thus, ordinary dietary sources usually provide ≈2.5 μg vitamin D/d, but can go as high as 5 to 10 μg with the use of fortified foods (90).

Dietary supplements

Many vitamin D-containing dietary supplements for adults are formulated to provide ≤5–10 μg/d, when used according to the label instructions. Although rare and not widely available, a few supplements now contain as much as 1250 μg vitamin D/d. Consumption of multiple dietary supplements with vitamin D, for example multivitamins and some calcium products, could produce higher intakes. Such intakes can exceed both the current FNB vitamin D UL of 50 μg/d and our proposed UL.

RISK CHARACTERIZATION

In conclusion, unfortified foods, fortified foods, and most dietary supplements, combined, do not contribute to a total exposure anywhere near the recommended vitamin D UL of 250 μg/d. 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 dietary supplements. Therefore, total exposure to vitamin D, including autogenous production under UV light stimulation, 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 concentration (≈500 nmol/L) that is well below the estimated concentration 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 2500 μg, have shown no toxicity if restricted to 1 occasion per 4 mo (21) or daily for a single period of 4 d (20).

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. These restrictive practices have served to effectively curtail research efforts and limit the public from deriving the most possible benefit from this nutrient. The conclusion that the present UL established by the FNB is lower than justified by the scientific evidence has been echoed by several experts in the field of vitamin D research (15, 44, 97–99). However, the present review is the first to provide a quantitative basis and recommendation for an actual revised UL value. Newer clinical trial data are sufficient to show 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.

JNH applied the risk assessment methodology. AS searched literature and summarized relevant findings. RV and RH contributed to literature citations as well as evaluated vitamin D effects. All authors interpreted the data, wrote the text, and reached the conclusions. JNH and AS are employed by a vitamin and dietary supplement industry trade association. RV and RH had no personal or financial conflicts of interest.

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