

Do we really need ≥ 100 μg vitamin D/d, and is it safe for all of us?

Dear Sir:

Vieth et al (1) regard a daily intake of ≥ 100 μg (4000 IU) vitamin D₃ necessary "to ensure desirable 25(OH)D [25-hydroxyvitamin D] concentrations." In their study, Vieth et al administered 100 μg vitamin D₃/d for ≤ 5 mo to 18–56-y-old healthy subjects living at high latitudes. They found that the mean serum 25(OH)D concentration plateaued at 96 nmol/L (with an extreme of almost 140 nmol/L) without concomitant changes in serum calcium or the urinary calcium-to-creatinine ratio, which were used as indexes of hypervitaminosis D. Vieth et al concluded that "consumption of vitamin D₃ at intakes ≥ 100 $\mu\text{g}/\text{d}$ causes no harm" and that the lowest adverse effect level is higher than the current estimate of 95 $\mu\text{g}/\text{d}$, as recognized by the Food and Nutrition Board.

We question whether there is at present any evidence-based medicine showing that a vitamin D intake of ≥ 100 $\mu\text{g}/\text{d}$ is necessary to prevent disease either in the short term or in the long run. There is evidence that lower doses (10–20 μg) improve bone mineral density (2–4) and reduce fracture incidence (3, 4). The quoted inverse relation between 25(OH)D and parathyroid hormone is well taken, but cannot be considered other than as an experimental target that may set the stage for an as yet to be conducted randomized controlled trial with hard endpoints, such as fracture incidence. The question is, who would need as much as ≥ 100 $\mu\text{g}/\text{d}$, because the physiologic plateau of ≈ 100 nmol 25(OH)D/L encountered by Vieth et al is surprisingly comparable with that obtained with much lower dosages in different settings (for review *see* reference 5). Dawson-Hughes et al (3) supplemented 70-y-old subjects with 17.5 μg vitamin D for 3 y to reach 25(OH)D concentrations of 112 nmol/L, and Chapuy et al (4) reached 104 nmol/L in 84-y-old women with a 20- μg supplement. Another example is the 108-nmol/L mean 25(OH)D concentration that was reached with 20 $\mu\text{g}/\text{d}$ in 74-y-old women who lived in the tropics and had high baseline 25(OH)D concentrations (6).

These findings raise questions regarding the fate of any excess vitamin D that becomes unconverted to 25(OH)D in persons who have been treated with ≥ 100 μg vitamin D/d. One option is accumulation in adipose tissue: rats treated with supraphysiologic vitamin D dosages show linear accumulation of vitamin D in their fatty tissue with time (7). Storage in adipose tissue is likely to be at the basis of the 100-nmol/L physiologic 25(OH)D plateau; this pool can apparently be mobilized because rats

deprived of food had higher 25(OH)D concentrations than did fed controls. These data suggest that daily intakes of 100 μg may be safe in the short run, but that prolonged consumption may, depending on baseline values, constitute a potential time bomb with an as yet poorly understood detonator.

We nevertheless tend to agree with Vieth et al that the dangers of hypervitaminosis D at moderate vitamin D doses are generally exaggerated. To remove this fear, fat-soluble vitamin toxicity studies may have to be based on long-term observations that also consider the tendency of these compounds to accumulate in the body. Any discussion of the results of such investigations should stress the many limitations of the study design, such as age group, supplement duration, background dietary intake, and background sunlight exposure, to prevent unintended extrapolation to other populations. It is all right to aim at those with the lowest initial status, but it is also right to remain inhibited by those with the highest.

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Reply to FAJ Muskiet et al

Dear Sir:

I welcome the commentary of Muskiet et al, who present what I see as 4 reasonable questions that probably reflect the thoughts of many readers of our recently published study (1).

1) Is there any evidence that a vitamin D intake of 100 µg/d is more beneficial than one of 20 µg/d? The answer is that no study has ever been attempted to show benefits of vitamin D beyond 20 µg/d. Concerns about vitamin D such as those exemplified by the preceding letter have made it difficult for anyone to be rigorous about the study of vitamin D nutrition in humans.

We cited 6 studies in our article that concluded that if the aim is to keep parathyroid hormone concentrations low, 25-hydroxyvitamin D [25(OH)D] concentrations should exceed 70 nmol/L (1). It remains hypothetical whether that 25(OH)D target level delivers tangible health benefits. Because a mean concentration at a target level implies that one-half of the study group has values below the target, it is important for researchers to know how to ensure that the target is met. Our article gives a realistic sense of how much vitamin D must be consumed to ensure what others consider desirable. In drug development, a phase 1 study like ours would be only the first clinical step. However, Muskiet et al question whether more developmental work is needed for vitamin D because some health benefits were detectable at lower doses.

A wealth of scientific literature, from fields ranging from epidemiology to molecular biology, provides compelling circumstantial evidence that the health benefits of vitamin D extend far beyond effects on just bone. If this kind of preclinical evidence were to exist for any patented molecule, clinical development would be much faster than it is with vitamin D, and it would not suffer from the arbitrary dose restrictions that have constrained nutritional research.

2) Similar 25(OH)D concentrations have been reported by others using 15–20 µg/d, so why use so much more? It is instructive to note that the 2 exceptions seem to be getting all the attention, whereas the majority of publications that pres-

ent lower 25(OH)D data for the same dose are ignored. At least 25 other studies in which ≈20 µg/d was used reported average 25(OH)D concentrations <80 nmol/L, as cited previously (2). More recent studies also report this finding. The 2 papers cited by Muskiet et al were the exceptions in terms of the 25(OH)D concentrations attained (3, 4) because they used the “direct” method of measuring 25(OH)D (5). Both laboratories have since stopped using the method, and Meunier (6) now reports lower 25(OH)D concentrations, in line with most of the literature.

3) What would happen if persons in the tropics with abundant sun exposure acquired 100 µg additional vitamin D/d? If serum 25(OH)D concentrations are already >150 nmol/L, then the effective physiologic supply of vitamin D is equivalent to ≈250 µg/d (2). The 25(OH)D response to a vitamin D dose behaves in a log-dose manner as shown in Figure 2 of my review (2). As a further example, we reported that 25 µg vitamin D/d resulted in average 25(OH)D concentrations of 69 nmol/L, whereas 4 times that amount increased 25(OH)D concentrations by only another 27 nmol/L (1). That increment becomes even smaller as the predose 25(OH)D concentration increases. Thus, an additional 100 µg/d would add marginally to what I regard as the inconsequential risk due to the 250-µg/d vitamin D supply that is physiologic because it is obtainable through sun exposure. Because all available evidence indicates that a long-term vitamin D consumption of ≥1000 µg/d is needed to cause hypercalcemia, there is a large margin of safety with 100 µg/d. [I welcome any discussion of evidence implicating harm with vitamin D₃ (not D₂) in adults at doses <1000 µg/d. There is simply nothing published about this, except in infants.]

4) Would vitamin D not accumulate in adipose tissue and cause toxicity if adipose tissue were to break down? In our study, we did consider the effect of body mass, but could not detect a correlation between weight and the effect of a vitamin D dose on serum 25(OH)D (1). Muskiet et al describe a study in which the investigators administered enough vitamin D to rats to raise circulating 25(OH)D and vitamin D to 1800 nmol/L, which is in the toxic range, and then measured vitamin D in fat tissue (7). There is a reason so much vitamin D ended up in the rats' adipose tissue. Pharmacologic amounts of vitamin D that are toxic pre-occupy circulating vitamin D binding protein; thus, the percentage of vitamin D that is free and unbound increases (2, 8). At toxic doses, the freely circulating vitamin D and its metabolites accumulate in both adipose (7) and muscle (9). The dosage of 100 µg vitamin D/d we used was physiologic and far below the amount that could change the free fraction of circulating metabolites as a result of saturation of vitamin D binding protein. Thus, the deposition of vitamin D in adipose tissue would be no more than what will occur for persons getting a lot of sun exposure. Before doing the human study, my laboratory looked at modest vitamin D supplementation in rats, in which we kept 25(OH)D concentrations well within the normal, human range. There were profound noncalcemic changes in the calcium homeostatic system, including higher tissue vitamin D receptor expression and PTH suppression (10). We used several strategies in the search for vitamin D in the adipose tissue of those rats, but at the doses we used, detected no vitamin D there. Because it was negative, that observation was not published.

I point out that pork and beef products are not meaningful sources of vitamin D nutrition unless the animals have been dosed

with enough vitamin D to cause hypercalcemia (7, 9). There is simply no reason to think that the amount of vitamin D in the adipose tissue of animals or humans without vitamin D-induced hypercalcemia should be a concern. In any discussion of vitamin D, we must maintain a context, and note what is physiologic and what reflects true excesses.

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Tolerable upper intake level of vitamin D

Dear Sir:

In their article on high doses of vitamin D, Vieth et al (1) provide data that are useful for evaluating vitamin D safety and

interpreting the practical meaning of the tolerable upper intake level (UL) (2). The objectives, design, and data presentation of the study are straightforward and appropriate. Although the comments in the introduction and discussion sections are generally appropriate, they warrant additional explanation to clarify and correct certain interpretations in the hope that the policy implications of their data will be fully appreciated.

Vieth et al state that “Food and Nutrition Board guidelines specify 50 µg/d as the highest vitamin D intake that healthy adults can consume without risking hypercalcemia [it is the upper limit, or the no adverse effect level (NOAEL)].” This statement is wrong in specific ways that should be corrected.

The Food and Nutrition Board (FNB) identifies 50 µg/d as the UL for vitamin D for most healthy adults (3). The UL is defined as “the maximum level of total chronic daily intake of a nutrient judged to be likely to pose no risk of adverse health effects to the most sensitive members of the healthy population” (2). The UL is derived by dividing the NOAEL by an uncertainty factor that is identified from a specific database. For vitamin D, the FNB applied an uncertainty factor of 1.2 to an NOAEL of 60 µg/d to calculate the UL as 50 µg/d. The UL is equal to the NOAEL only if the uncertainty factor selected is 1.0. Therefore, for vitamin D the UL is not equal to the NOAEL.

The FNB’s phrase “likely to pose no risk” is important. It does not mean that exceeding the UL by any amount will pose a risk. It correctly implies that the UL is an intake that should provide a comfortable margin of safety below the intakes that may cause adverse effects.

Vieth et al correctly state that the FNB identified 95 µg vitamin D/d as the lowest observed adverse effect level on the basis of data provided by Narang et al (4). The FNB characterized the severity of the adverse effect (hypercalcemia) observed by Narang et al at a vitamin D intake of 95 µg/d as “modest”; therefore, it is not surprising that the data from Vieth et al failed to show the modest adverse effect.

The modest adverse effects found by Narang et al at a vitamin D intake of 95 µg/d and the absence of adverse effects found by Vieth et al at a vitamin D intake of 100 µg/d indicate that the FNB’s UL of 50 µg vitamin D/d provides a substantial margin of safety below the intakes that might cause vitamin D toxicity in most healthy adults. The only policy implication of the data by Vieth et al is that the FNB may wish to consider revising and increasing the UL for vitamin D.

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Derivation of tolerable upper intake levels of nutrients

Dear Sir:

I am writing in my role as Chair of the Subcommittee on Upper Reference Levels of Nutrients of the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (DRI Committee) of the Food and Nutrition Board, Institute of Medicine (IOM) of the National Academies. My letter is occasioned by remarks in the February 2001 issue of the *Journal* in which Vieth et al (1) discussed the safety of vitamin D₃ and raised issues regarding the derivation and use of tolerable upper intake levels (ULs) for nutrients. I am not writing to raise questions about or to comment on the reported study. I am instead writing to clarify certain conceptual features of the model used to derive ULs and to ensure that the appropriate interpretation be given to the values derived for specific nutrients.

In their introductory paragraph, Vieth et al state that "Food and Nutrition Board guidelines specify 50 µg/d as the highest vitamin D intake that healthy adults can consume without risking hypercalcemia [it is the upper limit, or the no adverse effect level (NOAEL)]." Although 50 µg/d for vitamin D was the UL, it is important to recognize that the UL is not equivalent to the NOAEL of 60 µg/d. The purpose of this letter is to correct this misconception by clarifying the concepts and terminology used in the DRI reviews.

The DRI definition of a UL is "the highest daily level of chronic nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population" (2). The model developed and used to determine ULs is based on well established principles of risk assessment (2). The model relies on data concerning adverse health effects from excessive nutrient intakes in epidemiologic studies, clinical trials, and experimental studies. Several factors associated with these various data sources influence the derivation of a UL. Among the most important of these factors are the intake at which adverse effects are documented (ie, the LOAEL, or lowest observed adverse effect level) and the maximum level of intake, which is always less than the LOAEL, at which no adverse health effects are observed (the NOAEL). In some studies both an LOAEL and a NOAEL are documented, and in others only an LOAEL is reported. Both the LOAEL and NOAEL are derived from studies of excess nutrient intakes. The UL is not a data point but is strictly a derived value; in almost all cases, it is less than an observed NOAEL.

Risk assessment practice requires that judgments be made regarding the limitations of the data that are the sources of the NOAEL and LOAEL (3). To derive a UL, uncertainty factors are introduced to account for the uncertainties associated with extrapolating from the observed data to a healthy population. Applying uncertainty factors to an NOAEL (or LOAEL) will result in a value for the UL that is less than the experimentally

derived NOAEL, unless the uncertainty factor is 1.0.

Those who make use of UL information should consult the chapter in each of the DRI reports that describes the model for UL development (eg, in reference 2, chapter 3, which provides DRIs for vitamin D). The chapters describe in detail the basis for selecting data for UL development and for the various uncertainty factors used to derive a UL from an NOAEL (or, if the latter is not available, from the LOAEL).

Vieth et al also raise the concern that research proposals to study nutrients in clinical trials at doses that exceed the LOAEL (and, presumably, even at doses that exceed the UL) may be looked on unfavorably by ethical review panels, funding agencies, and even study subjects. Concerning this issue, a recent report of the DRI Committee specifically comments, "In light of evaluating possible benefits to health, clinical trials of doses above the UL should not be discouraged, as long as subjects participating in these trials have signed informed consent documents regarding possible toxicity, and as long as these trials employ appropriate safety monitoring of trial subjects" (4).

Intakes greater than a UL may present a risk of adverse effects to sensitive members of the general population. The potential for actually being at risk (the number of affected individuals) increases as doses reach and exceed the NOAEL, and risk is expected at the LOAEL; however, not everyone will actually be adversely affected at intakes in excess of the UL. Clinical trials conducted under medical supervision and with patient consent can be planned and conducted ethically as long as the potential subject risk is understood and appropriate medical precautions are taken. The IOM reports on individual nutrients provide information on the types of possible effects that might be expected. The ULs and the recommended dietary allowances (5) are derived primarily to assist in dietary planning and counseling for free-living (nonmedically supervised), apparently healthy individuals.

The data specific to vitamin D that are reported by Vieth et al were not available at the time the UL for vitamin D was derived. The new study was, as the authors noted, developed in response to concerns raised about the data used to derive the UL. The authors are applauded for having undertaken this investigation, and had their work been available for evaluation, it might have influenced the outcome. The process of establishing DRIs requires that only published data be used, so consideration of the data reported by Vieth et al will come at the time of a future IOM review. Other investigators are urged to follow the lead of Vieth et al because it has become clear during this initial systematic IOM review of the adverse health effects of excessive nutrient intake that more complete data, developed with appropriate investigational methods, are sorely needed for many nutrients.

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Reply to J Hathcock and I Munro

Dear Sir:

I agree with the clarification that the tolerable upper intake level (UL) for vitamin D is 17% lower than the no observed adverse effect level (NOAEL). The distinction was omitted from our article (1) for the sake of brevity, but it should have been explained as Hathcock and Munro did in their letters. My comment is that, despite the theoretical principles for deriving the UL for each nutrient, the Food and Nutrition Board (FNB) did not give a reason why the uncertainty factor for vitamin D was chosen other than to state that the value was "conservative" (2). Therefore, it appeared to me that the 17% adjustment was simply adopted to produce a value equal to the vitamin D safety limit of 50 µg/d (2000 IU/d) that was referred to in earlier FNB reports since at least the 1968 edition of *Recommended Dietary Allowances* (3).

Unlike the ULs for most other nutrients, the UL for vitamin D is not internally consistent across age groups. According to the model for deriving ULs, adjustments rely on body weight ratios (4). On the basis of what is probably a more rigorously established UL for vitamin D for infants and assuming a body weight ratio of 10, the infant data imply that the adult UL should be 250 µg/d; this value is within the adult physiologic production rate for vitamin D (5).

Munro emphasizes the need for published evidence, but we must recognize the reality of a publication bias that ignores or downplays safety and highlights evidence of harm. To illustrate this, evidence for the safety of doses of vitamin D higher than the current lowest observed adverse effect level (LOAEL) was presented in papers published before 1995, when this issue was last reviewed by the FNB. I know of 2 articles that, although they did not focus on the issue, clearly showed that high doses of vitamin D do not cause hypercalcemia in healthy subjects (6, 7). Neither article was mentioned in the FNB review that set upper limits (2). I reviewed at least 3 other studies of healthy subjects in which doses of vitamin D exceeded the NOAEL (5). Although those studies do not mention hypercalcemia, I suggest that it did not occur in those studies either. Any other interpretation implies that the authors failed to consider the effects of vitamin D on calcium or neglected to mention evidence of toxicity; it is hard to imagine either scenario. Instead, authors are inclined to take for granted aspects of nutritional studies showing that no harm was done, and authors do not highlight noneffects (safety) in their publications. Furthermore, because evidence for safety is difficult to support by statistical analysis and

because statements about safety are easy prey for critics, such statements are usually eliminated from publications. Thus, the issue of safety may not necessarily require more research designed to provide data for the process of establishing DRIs. Instead, researchers and those involved in the review and publication process should be aware of the need to place more emphasis on the implications of study results for both safety and toxicity.

A report by Barger-Lux et al (8) is particularly relevant because they found no hypercalcemia in 14 men taking 1250 µg vitamin D₃/d for 8 wk; this dosage is 10 times the highest cumulative dosage purportedly given by Narang et al (9). [One of the authors of that study (9) was a member of the appropriate UL subcommittee of the FNB and would have known of this work, which was unpublished at the time the UL was set.] When the data of Barger-Lux et al (8) are taken in the context of Haber's law (toxic efficacy reflects dose times its duration), the evidence against the current UL or NOAEL becomes overwhelming. Haber's law is applied by the Food and Drug Administration to facilitate comparisons among studies that used different dosing protocols, to help establish reference doses (10).

Hathcock states that the change in serum calcium with 95 mg vitamin D/d (the LOAEL) was described by the FNB as "modest," ie, small and statistically difficult to detect. However, on page 282, the final FNB report uses the word *modest* in the context of the calcium change that Narang et al (9) evoked with 30 mg vitamin D/d (2). Because the article by Narang et al (9) is not readily available but is the only article used by the FNB to define the current UL, NOAEL, and LOAEL, some of its data are reproduced here for comparison (**Table 1**). Our study had the power to detect an increase in serum calcium as small as 0.06 mmol/L, well within the capability of detecting the 0.19-mmol/L increase (2.62 – 2.43 mmol/L; $P < 0.01$) that Narang et al (9) reported with 60 mg vitamin D/d. The LOAEL was based on mean serum calcium in the hypercalcemic range, 2.83 mmol/L (11.3 mg/dL), not on a modest increase.

TABLE 1

Doses of vitamin D pertinent to the tolerable upper intake level (UL) and the lowest observed adverse effect level (LOAEL) and their effects on serum calcium¹

Vitamin D [µg (IU)/d]	Serum calcium	
	Narang et al (9) ²	Vieth et al (1) ³
	<i>mmol/L</i>	
0	2.43 (2.29, 2.57)	2.38 (2.36, 2.41)
60 (2400)	2.62 (2.39, 2.84) ⁴	—
95 (3800)	2.83 (2.61, 3.05) ⁵	—
100 (4000)	—	2.40 (2.38, 2.43)

¹ \bar{x} ; 95% CI in parentheses. 95% CIs were calculated by adding and subtracting from each mean the values derived by multiplying the SEM by the t value where the two-tailed t value for $n = 6$ is 2.447.

²The mean of 6 healthy control subjects at baseline (initial values for those given 95 µg of an unspecified form of vitamin D/d) and of 6 subjects per group after 3 mo of treatment. Adapted from reference 9.

³The mean of 32 subjects at baseline and 23 subjects after 3 mo of treatment with vitamin D₃. Adapted from reference 1.

⁴Significantly different from baseline, $P < 0.01$ (presumably paired t test). This result is the basis of the current no observed adverse effect level and of the current UL.

⁵Significantly different from baseline, $P < 0.02$ (presumably paired t test). This result is the basis of the current LOAEL.

I was pleased that Munro mentioned our comments about the research limitations created by the current UL for vitamin D. Despite the clarification about the UL in the preceding letters, health professionals tend to regard the UL as the toxic dose. They think of vitamin D as a drug, for which the UL is the numerator used to calculate the therapeutic index (ratio of the toxic dose to the effective dose). For example, at the adequate intake (AI) of 15 $\mu\text{g}/\text{d}$ for older adults, the perceived therapeutic index for vitamin D is only 3.3. Of the 71 hospital workers who served as subjects in our study, only 1 was a physician. Saying that they did not consider it prudent to take >50 mg vitamin D/d, other physicians declined invitations to take part in the study. The FNB has not made it clear to health professionals that the LOAEL (not the UL) should be used as the numerator in calculations of the therapeutic index for nutrients. As a result, pharmacists almost always warn patients against taking the highest dose of vitamin D available over the counter (25 $\mu\text{g}/\text{pill}$, 1000 IU). They are warning patients against taking the very dose that adults need to ensure that 25-hydroxyvitamin D concentrations exceed the decision point for vitamin D insufficiency (11). To see first-hand the real-life effect of the current UL for the public, I suggest that readers pose a naive question to their local pharmacist about the risk of taking the 1000-IU vitamin D pills.

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