
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 D, 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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REFERENCES
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 D/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

<table>
<thead>
<tr>
<th>Vitamin D [μg (IU)/d]</th>
<th>Narang et al (9)</th>
<th>Vieth et al (1)</th>
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<tbody>
<tr>
<td>0</td>
<td>2.43 (2.29, 2.57)</td>
<td>2.38 (2.36, 2.41)</td>
</tr>
<tr>
<td>60 (2400)</td>
<td>2.62 (2.39, 2.84)</td>
<td>—</td>
</tr>
<tr>
<td>95 (3800)</td>
<td>2.83 (2.61, 3.05)</td>
<td>—</td>
</tr>
<tr>
<td>100 (4000)</td>
<td>—</td>
<td>2.40 (2.38, 2.43)</td>
</tr>
</tbody>
</table>

1: 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.

2: The 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.

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

4: Significantly 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.

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