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.

Reinhold Vieth

Department of Laboratory Medicine and Pathobiology
University of Toronto and
Pathology and Laboratory Medicine
Mount Sinai Hospital
600 University Avenue
Toronto, Ontario M5G 1X5
Canada
E-mail: rvieth@mtsinsai.on.ca

REFERENCES

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.

John Hathcock

Council for Responsible Nutrition
1875 Eye Street, NW
Suite 400
Washington, DC 20006-5409
E-mail: hathcock@crnusa.org

REFERENCES

**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 participants 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.

Ian Munro

Food and Nutrition Board
Institute of Medicine
2101 Constitution Avenue, NW
Washington, DC 20418
E-mail: fnb@nas.edu

**REFERENCES**