

Symposium: Optimizing Vitamin D Intake for Populations with Special Needs: Barriers to Effective Food Fortification and Supplementation

Critique of the Considerations for Establishing the Tolerable Upper Intake Level for Vitamin D: Critical Need for Revision Upwards¹

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ABSTRACT The tolerable upper intake level (UL) for vitamin D is 50 mcg/d (2000 IU/d) in North America and in Europe. In the United Kingdom a guidance level exists for vitamin D, 25 mcg/d (1000 IU/d), defined as the dose “of vitamins and minerals that potentially susceptible individuals could take daily on a life-long basis, without medical supervision in reasonable safety.” Exposure of skin to sunshine can safely provide an adult with vitamin D in an amount equivalent to an oral dose of 250 mcg/d. The incremental consumption of 1 mcg/d of vitamin D₃ raises serum 25-hydroxyvitamin D [25(OH)D] by ~1 nmol/L (0.4 µg/L). Published reports suggest toxicity may occur with 25(OH)D concentrations beyond 500 nmol/L (200 µg/L). Older adults are advised to maintain serum 25(OH)D concentrations >75 nmol/L. The preceding numbers indicate that vitamin D₃ intake at the UL raises 25(OH)D by ~50 nmol/L and that this may be more desirable than harmful. The past decade has produced separate North American, European, and U.K. reports that address UL or guidance-level values for vitamin D. Despite similar well-defined models for risk assessment, each report has failed to adapt its message to new evidence of no adverse effects at higher doses. Inappropriately low UL values, or guidance values, for vitamin D have hindered objective clinical research on vitamin D nutrition, they have hindered our understanding of its role in disease prevention, and restricted the amount of vitamin D in multivitamins and foods to doses too low to benefit public health. *J. Nutr.* 136: 1117–1122, 2006.

KEY WORDS: • *vitamin D* • *cholecalciferol* • *hypercalcemia* • *tolerable upper intake level*
• *25-hydroxyvitamin D* • *toxicology*

The following discussion focuses on the inadequacies of the current upper intake level (UL)³ value for vitamin D and the potential public health benefits of a proposed higher tolerable

upper-intake level for this unique fat-soluble vitamin. Unlike the slow, subtle effects of most vitamin excess, vitamin D overdose is unambiguously evident by hypercalcemia, dehydration, and tissue calcification (1–4). Furthermore, no other nutrient has a long history of use as a rodenticide (5). These features combine to make vitamin D a good example of why care should be taken to avoid excessive intake of vitamins. While safety is, of course, an important issue, the definition of what constitutes an “excessive intake” of vitamin D remains so ambiguous that it may affect the ability of the public to obtain supplements with doses of vitamin D that are appropriate for health.

The vague terminology of vitamin D safety. The Institute of Medicine, through a Canadian/United States Subcommittee on Upper Reference Levels of Nutrients and the European Commission’s Health and Consumer Protection Directorate-General, defines a tolerable upper intake level as 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 (6,7). The United Kingdom’s EVM (Expert Group on Vitamins and Minerals) may specify a “safe upper limit,” but it did not establish such a value for vitamin D. Instead, the EVM offered a guidance level for vitamin D, defined as “doses

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³ Abbreviations used: LOAEL, lowest-observed-adverse-effect-level; NOAEL, no-observed-adverse-effect-level; RDA, recommended dietary allowance; SUL, safe upper limit; UL, tolerable upper limit; UF, uncertainty factor; 25(OH)D, 25-hydroxyvitamin D.

of vitamins and minerals that potentially susceptible individuals could take daily on a life-long basis, without medical supervision in reasonable safety" (8; p. 6).

The UL is important because its purpose is to ensure public safety, but one might question whether the UL value established for vitamin D fulfills this purpose. Over the past decade, an "excessive intake" of vitamin D has come to be defined for most people by the UL; however, this has never been the meaning intended for the UL. The definition of the UL is ambiguous, based more on what it is not, than on what it is. A better alternative, applied to some nutrients in the U.K., is the safe upper limit (SUL). "SULs or Guidance Levels are the doses of vitamins and minerals that susceptible individuals could take daily on a life-long basis, without medical supervision. The levels have been derived so that the consumer can have confidence that harm should not ensue from daily intake up to that level" (8; p. 23). The SUL is an assurance of safety. Remarkably, the EVM does not define a safe level for vitamin D, and has offered a "guidance level" instead. For vitamin D, the EVM document explains the guidance level with terminology similar to the way the UL is defined, where the intake of 25 mcg/d (1000 IU/d) "would not be expected to cause adverse effects in the general population" (8). In the EVM document, the guidance level is an assurance of safety, but it is this way with less certainty than the criteria needed for an SUL [this would account for why its uncertainty factor is so large, as discussed later]. The UL, SUL and guidance level are all well-intentioned guides for the general public. Unfortunately, they are not straight forward, and for vitamin D in particular, they hinder the implementation of scientific evidence that adults require more vitamin D than previously thought.

Nutritional adequacy for vitamin D is measured, based not on intake from food or supplements, but rather upon serum 25-hydroxyvitamin D [25(OH)D] concentrations. In Europe, the Scientific Committee on Food based its UL upon the 100 mcg/d dose of vitamin D₃ that produced 25(OH)D levels as high as 150 nmol/L (9,10). It then applied an uncertainty factor (UF; a factor divided into the no-observed-adverse-effect-level to obtain the UL) of 2, ending up with a UL of 50 mcg/d (7). All bodies that have specified a UL for vitamin D specifically avoid the question of whether an intake more than the UL is safe or harmful.

The UL has taken on implications beyond its intended purpose "to assist in dietary planning and counseling for free-living (nonmedically supervised), apparently healthy individuals" (11; p. 865). Whether intended or not, at least 5 interest groups are affected by the UL (Table 1). Each group draws different implications from the UL for vitamin D. One implication is that the UL for vitamin D plays a major role in determining the dosage suitable for nutrition research. There

are several examples of this limitation on research (12–14). In theory, the UL is based upon knowledge gained through research. However, the UL does affect the kind of research that helps to determine the UL.

The top panel of Figure 1 summarizes the classic concepts behind dietary recommendations. For this, the risk of harm is represented by the height of the curved lines above the horizontal axis. The left vertical axis represents risk of harm from insufficiency, the right axis represents risk of harm due to excess. The UL is obtained by adjusting the no-observed-adverse-effect-level (NOAEL) downward by dividing by a UF. The UF is intended to reflect a conservative approach, to compensate for possible inadequacy of data. In theory, as more data become available, uncertainty should decrease. The NOAEL is usually much less than the lowest-observed-adverse-effect-level (LOAEL). A summary of the considerations for safe upper limits of nutrients as outlined by the relevant bodies (Table 2) (6–8), is further explained by Walter (15).

Unrealistic hypothetical curves for risk of vitamin D deficiency and excess. The fundamental assumption is that, for all nutrients, there is a wide gap between risk of nutrient inadequacy and the risk of nutrient excess (Fig. 1). The flat section of the graph is entirely hypothetical and may or may not be relevant to vitamin D. A wide gap between adequate and excessive intake is used to justify why committees that evaluate nutrient requirements are usually different and separate from the committees that evaluate excess (6–8). A narrow gap (like that represented by the middle panel of Fig. 1) would force committees to balance risks and benefits, instead of addressing each without regard for the other.

To date, committees that address the issue of vitamin D safety have failed to address the possibility that a narrower minimum risk zone (as is hypothetically represented by the middle panel of Fig. 1) might be appropriate. The current dilemma with respect to vitamin D is how to deal with a UL that is 50 mcg/d in light of accumulating evidence that the total daily adult requirement may be 100 mcg/d (16).

Failure to define what is a physiologic "intake" of vitamin D. For vitamin D, the nutritional value is not straightforward. For example, the British EVM document does not define the nutritional value for any nutrient, let alone for vitamin D (8). Because very few foods naturally contain vitamin D, the conventional definition of the term nutrient can be challenged. The definition of adequate intake is an "observed or experimentally derived intake by a defined population or subgroup that, in the judgment of the DRI Committee, appears to sustain a defined nutritional state, such as normal circulating nutrient values, growth, or other functional indicators of health". Adequate intake is a "judgment" made necessary by the lack (6; p. 315) or absence of the quality of evidence necessary for

TABLE 1

Influence of the UL on actions and policies of key interest groups

Medical and health advisors, and the general public.	The UL plays a major role in determining what the public can be advised to take without a prescription. It specifies the point beyond which pharmacists advise customers that vitamin D can be toxic.
Dietary supplement industry.	The UL limits the amount of vitamin D that manufacturers may provide in a daily dose to the general public in over-the-counter products.
Legal profession.	The UL defines the vitamin D level beyond which legal counsel can argue that a product is unsafe or substantiate that the product has the potential to cause harm due to excessive vitamin D content.
Clinical nutrition researchers.	The UL plays a powerful role in the dosage that can be used for nutrition research even though "physiologic" supplies of vitamin D via the skin reach above 250 mcg/d. Vitamin D is classified as a drug in Europe if the dose is over 10 mcg/d, and in North America if the dose is over 25 mcg/d.
Research ethics committees and government oversight.	For "drug" studies, additional monitoring is mandated that limits enrollment and increases cost of clinical studies at doses higher than the UL. Consequently, the UL defines and limits the dose of vitamin D that is feasible for clinical nutrition research.

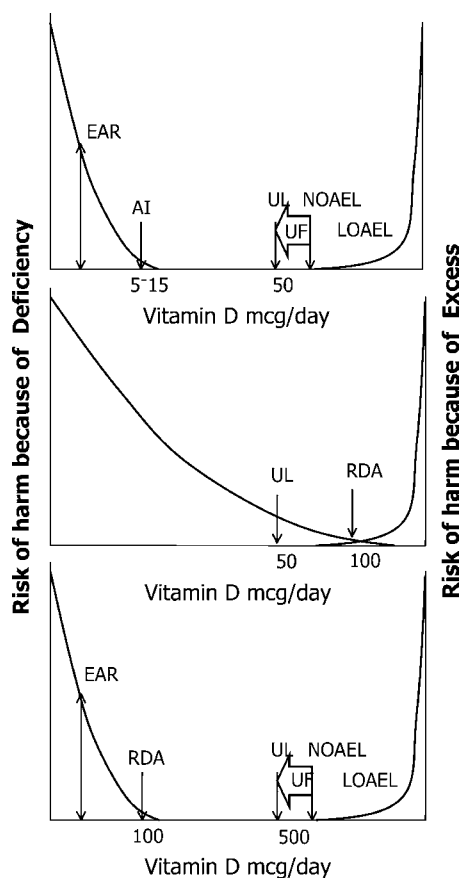


FIGURE 1 (Top) Representation of nutrition terms relevant to vitamin D according to Yates et al. (53). The abbreviations represented are: EAR, estimated average requirement (for vitamin D); AI, adequate intake; UL, upper level (calculated by dividing NOAEL by UF); NOAEL, no observed adverse effect level; UF, uncertainty factor; LOAEL, lowest observed adverse level. (Middle) The middle panel represents a different set of relations for deficiency and excess. The graph illustrates a hypothetical situation implied by combining the current UL with some of the recent evidence of adult requirements (16). This relation implies that some healthy adults require vitamin D in an amount that might be adverse to others. For health policy, the overlapping curves for deficiency and excess complicate decisions by making it necessary to balance risks and benefits. The possibility of this scenario has not been addressed in assessments of vitamin D safety (6–8). (Bottom) Represents what the author proposes may be the accepted reality for vitamin D in the future, based on an RDA that reflects the vitamin D supply from physiologic sun exposure of adults, and data on dose tolerability.

establishing a recommended dietary requirement (RDA) (6). This adds another dimension of complexity to the dilemma from the preceding paragraph. As long as the UL prevents healthy adults from consuming an amount of vitamin D that can produce the serum 25(OH)D concentrations (associated with health benefits in epidemiologic studies of vitamin D-deficient adults), it will be difficult to design studies of a quality suitable for establishing RDA levels for vitamin D. The objective index for vitamin D adequacy is the serum concentration of 25(OH)D (6). A recent consensus suggests that desirable 25(OH)D values exceed 75 nmol/L (17). An adult who regularly consumes the UL for vitamin D will increase serum 25(OH)D by ~50 nmol/L (18). The arithmetic suggests that the UL and the U.K.'s guidance level for vitamin D are too low, possibly even too low for the criteria for an RDA. This field begs for a reassessment by the Food and Nutrition Board. An

argument for raising the RDA for elderly adults has been presented in this symposium (19).

The nutritional value for vitamin D should be defined as an amount of vitamin D equivalent to what an adult can acquire through exposing full skin surface to summer sunshine. That is, a physiologic intake of vitamin D for an adult might range upward to 250 mcg/d (20–22).

For every other nutrient, a physiologic amount is the quantity acquired by eating a normal diet. What makes vitamin D different is that supplementation or fortification is intended to compensate for a deficiency of sunshine (23,24). Furthermore, “pharmacologic” is not necessarily “toxic.” The effects of higher doses of vitamin D₃ (in contrast to vitamin D₂) need to be characterized far better than they are now.

To date, most preparations of prescriptions for high-dose vitamin D have been in the form of vitamin D₂, a compound that is not commonly present in foods or in primate circulation, and which has been shown to be less effective in raising serum 25(OH)D than vitamin D₃ when tested in humans (25–27). Vitamin D₃ is now the most common form used in over-the-counter dietary supplements and in food fortification in the U.S. and Canada. Food-related deliberations about the safety of vitamin D supplementation should focus specifically on evidence pertaining to vitamin D₃ as the natural, physiologic product.

UL considerations: hazard identification. Hypercalcemia is the classic criterion for determining vitamin D excess. Hypercalciuria can occur at lower doses of vitamin D than those that cause hypercalcemia (28). The cause of hypercalciuria is difficult to address. Although a higher serum 25(OH)D is associated with higher intestinal calcium absorption, this effect reaches a plateau at 75 nmol/L (19). Furthermore, according to epidemiologic evidence, there is no relation between vitamin D intake and the incidence of hypercalciuria (29).

The mechanisms by which vitamin D is toxic at the molecular level have been reviewed (30). In short, the mechanisms of toxic action for vitamin D, the nutrient, are probably due to saturation of the binding sites on vitamin D-binding protein in plasma, which has a total capacity for vitamin D metabolites of ~4700 nmol/L (31). Furthermore, it is impossible to turn off completely the 1-hydroxylase enzyme that is driven through mass action by 25(OH)D. The high concentration of “free” 1,25(OH)₂D, despite a normal total 1,25(OH)₂D concentration, is the mechanism by which the hypercalcemia of sarcoidosis is achieved (2). Another mechanism of toxicity involves the limited capacity to adapt metabolic clearance of vitamin D to eliminate metabolites from the body.

The quality and completeness of the data that support the current NOAEL and LOAEL are highly questionable. Official reports tend to focus on studies by Narang et al. (32) and Johnson et al. (33), which support the risk of harm at intakes around the current UL. The problems with the study by Narang et al. have been thoroughly dealt with elsewhere (10,34). The Johnson et al. (33) abstract mentions that 2 of 63 vitamin D-supplemented patients developed hypercalcemia, but none of the 40 placebo patients developed hypercalcemia. Although the difference in incidence of hypercalcemia is certainly not significant ($P = 0.52$), the Johnson publication is the main justification for British conservatism about vitamin D UL(8). Another article highlighted by the EVM is by Honkanen et al. (35), who supplemented free-living adults and institutionalized elderly with 45 mcg/d (1800 IU/d) of vitamin D. Honkanen et al. did not detect a change in serum calcium, yet they present their study as if there were potential for harm with vitamin D. This is despite the fact that the only 3 hypercalcemic subjects in their study were in the placebo group! This aspect of the Honkanen

TABLE 2

Process for establishing the safe upper limits for nutrients

1. Hazard identification through the collection, organization, and evaluation of all information pertaining to the adverse effects of a given nutrient. Animal studies may be of importance, but the key issue is evidence of adverse effects in humans.

Important criteria:

- a) proof of causality
- b) route of exposure (oral, dermal exposure, etc.)
- c) duration of exposure (acute vs. chronic)
- d) mechanisms of toxic action
- e) the quality and completeness of the database
- f) identification of highly sensitive subpopulations

2. Characterizing the dose-response between nutrient intake and adverse effect:

- a) human data are preferable, but animal data are relevant
- b) estimate the highest intake at which no adverse effect has been observed (NOAEL)
- c) estimate the lowest intake at which an adverse effect has been identified (LOAEL)
- d) take into account the range of nutrient intakes among members of a healthy population

3. Use judgment for setting the uncertainty factor (UF). Estimate the uncertainties and establish the UF for extrapolating the observed data and applying it to the risk for the general population:

- a) the larger the uncertainty, the larger the UF and the smaller the UL (the corollary is that UF should become less over time as more data become available)
- b) if most data are from human studies, the UF will be lower than five
- c) if animal studies are the main source of evidence, the UF value may go up to ten
- d) if a NOAEL value cannot be established, the UF may also be applied to a LOAEL value (a general observation is that estimated NOAELs are approximately one-third the LOAEL)

report was overlooked by the EVM (8). If one combines the 2 hypercalcemic patients taking vitamin D from the Johnson et al. study with the 3 hypercalcemic patients in the placebo group from the Honkanen et al. study, it becomes clear that consumption of vitamin D at ~50 mcg/d (2000 IU/d) contributes no adverse effect whatsoever. The traditional definition of hypercalcemia is a serum- or plasma-calcium level that is higher than the 97.5th percentile of levels in a normal population. Because the studies of both Johnson et al. and Honkanen et al. involved >100 patients, the number of subjects whose calcium bounced into hypercalcemic levels agrees with what could be expected for any population, especially an older one. There are well-described studies that confirm safety of vitamin D₃ intakes at 100 mcg/d (10,36) and at 250 mcg/d (37,38).

Probably the most helpful publications from a public-health perspective about the risks of vitamin D intake are those concerning the case of a home-delivery dairy in Boston that served 11,000 households with over-fortified milk containing highly variable amounts of vitamin D (39,40). Based on the dairy's purchase records of vitamin D, the average quart of milk contained 300 mcg/quart (12,000 IU/quart) between 1985 and 1991. However, the error, due to bad dispensing equipment for vitamin D, ranged upward as high as 6000 mcg/quart (while normal is 10 mcg/quart). Blank et al. reported that there were 56 cases of suspected or confirmed vitamin D intoxication (40). The most susceptible members of the population were women over the age of 69, infants, and children. If the current UL or the LOAEL for vitamin D were true, there have been far more cases of hypercalcemia.

UL considerations: the dose-response relation

Human studies. Several reports of industrial-scale mishaps have resulted in hypercalcemia (1-4). In the iatrogenic context, the lowest intake of vitamin D associated with hypercalcemia has been with a dose of vitamin D₂ of at least 40,000 IU/d (1000 mcg/d) for several months (20). Patients given regular bolus doses of vitamin D₃ [7500 mcg/wk (300,000 IU/wk)] can also develop hypercalcemia (41). This hypercalcemia was associated with 25(OH)D levels >1000 nmol/L. However, hyper-

calcemia can occur with 25(OH)D levels as low as 355 nmol/L (42).

Heaney et al. (38) studied the effects of increasing doses of vitamin D. He found that an incremental increase in vitamin D₃ increases the serum 25(OH)D by ~1.0 nmol/L when 25(OH)D levels are low, but this increment of mcg/d declines as the 25(OH)D increases beyond 100 nmol/L (18).

Animal studies. The most complete dose-response study published is that of Shepard and DeLuca (43). They gave groups of rats 10-fold increments of vitamin D₃ dosages. The highest dose that did not produce hypercalcemia was 65 nmol/d · rat⁻¹, this works out to 25 mcg/rat (1000 IU/rat). If we assume that they used relatively large rats, this becomes 50 mcg/kg (2000 IU/kg). If one then uses the 10-fold uncertainty factor for between-species comparisons, these rat data imply that, for an adult human, the NOAEL is ~250 mcg/d (10,000 IU/d). Using the same comparison, Shepard and DeLuca's study (43) suggests that adult human LOAEL may be ~10 times more than that.

High-vitamin D dosage studies have recently been reported for Great Dane dogs. Nineteen weeks of supplementation at 1350 µg/kg did not change serum-calcium levels (44). The resulting serum 25(OH)D concentration was 1255 nmol/L. By dividing the dog dose by 10, to account for the different species, this translates to a NOAEL human equivalent of 135 mcg/kg. This value suggests a wide margin of safety in dogs, but such a dose is implausibly high in the human context.

UL considerations: use of judgment

The concept of a UL for nutrient intakes has been implemented formally for only a decade. However, RDA reports before the 1990s did address the issue of vitamin D safety. The progression of historical statements relating to safe and toxic vitamin D intakes are summarized in **Table 3**. The first mention of the value that is the current North American/European UL of 50 mcg/d (2000 IU/d) was the statement in the RDA of 1964, that 50 mcg/d (2000 IU/d) may be a limit for infants (45). Because of a lack of evidence to the contrary, this same value was later extended to adults (46). That value, 50 mcg/d (2000

TABLE 3

Historic review of specific statements about toxic and tolerable vitamin D intakes for adults

Report year	LOAEL	NOAEL	UL	UF
	mcg/d	mcg/d	mcg/d	
NB 1958 (52)	No mention of safety		None	
FNB 1964 (45)	1250–3750 ¹		None	None
FNB 1968 (46)	None	50–75 ²	None	None
IOM 1997 (6)	96	60	50	1.2
EC 2002 (7)	None	100	50	2.0
EVM 2003 (8)	None	100	25	4.0 ³

¹ Adjusted to 50 kg body wt, according to the statement “Excessive quantities of vitamin D (of the order of 1,000 to 3,000 IU/kg/d) are toxic” (45; p. 25).

² “There is no evidence that intakes in the order of 2000–3000 IU/d produce hypercalcemia beyond infancy” (46; p. 26) i.e., the historic precedent in North America that 50 mcg/d (2000 IU/d) may be a safe upper limit.

³ This is a guidance level and not quite a UL. Although the British EVM group would not specify an uncertainty factor for vitamin D (p. 143 of its report) (8), the value 4, above, is the de facto uncertainty factor. This is because 100 mcg/d was the highest dose stated as safe, followed by the statement, “a level of 0.025 mg/d supplementary vitamin D would not be expected to cause adverse effects in the general population.” The EVM group obfuscated the issue of safety by focusing on the mention of 2 hypercalcemic subjects in the vitamin D group of Johnson et al. (33; p. 139), but they overlooked the 3 hypercalcemic subjects in the placebo group of Honkanen et al. (35). There is no evidence that vitamin D intake at 50 mcg/d causes hypercalcemia at a higher rate. This lack of evidence now extends to 275 mcg/d (38).

IU/d), has remained the focus of vitamin D safety committees ever since.

Since 1968, the adult safety limits for vitamin D, be they general comments, guidance levels, or UL values, have remained in the range of 25–50 mcg/d (6–8,46,47). In theory, the UF should become smaller as evidence accumulates. However, looking at Table 3, it is evident that, rather than raising the UL for vitamin D in accordance with data that shows higher intakes are safe, the UL has remained the same, and the change in response to this new evidence has been to raise the UF. Hence, the message the public has received concerning the UL or the guidance level for vitamin D has not been affected by new knowledge in the field for close to 40 years.

The concern that harm can result from combining a high intake of vitamin D with abundant sun exposure must be addressed. Based upon reports of patients intoxicated with vitamin D₃, we know that it requires 25(OH)D levels of >700 nmol/L to cause an undesirable change in calcium homeostasis (2,4,20,39). There is a potential risk of vitamin D intoxication in adults receiving abundant sunshine that, by itself, provides a safe amount of vitamin D (6–8). These adults may be theoretically more susceptible to toxicity when taking vitamin D supplements because of the cumulative effect from supplements and sun. American outdoor workers acquire a sun-derived vitamin D equivalent to consuming ~100 mcg/d (21). Although sun exposure delivers a moderate dose compared with doses safely used clinically, judgment in relation to a UL for vitamin D should account for sunshine.

There are rare individuals, such as those with sarcoidosis or tuberculosis, who should avoid both sunshine and vitamin D (48). However, this should be balanced against the possibility that the incidence of these diseases may be higher because of prevailing vitamin D insufficiency. One should ask whether the

upregulation of 1-hydroxylase within tissues represents a form of vitamin D hunger (49), and that with chronic upregulation of 1-hydroxylase, some cells lose the ability to downregulate 1,25(OH)₂D production once the substrate becomes available. There has also been a long-standing assumption that patients with primary hyperparathyroidism may be hypersensitive to vitamin D (8,50). However, recent work indicates that administering vitamin D to patients with primary hyperparathyroidism is noncalcemic, and that it suppresses PTH secretion and bone turnover (51).

Effect of committee psychology on the uncertainty factor

The analysis in Table 3 can only be explained as a psychological barrier that historic safety limits for vitamin D impose on the judgment of subsequent committees. In a group setting, the easiest way for anyone with good intention to exhibit good judgment is to be conservative. Anyone who proposes an increase in the UL will have to face others who see this as a move in the direction of greater danger (54). The path of least resistance is to avoid a change to the UL. This becomes very easy for a group to accept because the considerations and guidelines that UL committees must follow explicitly ignore any possibility that a low UL might be a problem in itself. The wide, flat gap in classic figures that illustrate risk-of-deficiency and risk-of-excess curves makes it easy to imagine that a UL will have no consequence for setting an eventual RDA (Fig. 1, top). The British report explicitly states that the “EVM has not conducted risk/benefit analyses of the nutrients since beneficial effects in excess of the nutritional value of the vitamins and minerals are not within its remit” (8; p. 130). The psychology and the evidence in Table 3 indicate that committees who are considering the safety of vitamin D adapt to new knowledge that higher doses are safe by raising the uncertainty factor instead of raising the UL.

The process of ignoring evidence of the true nutrient requirement has resulted in an unrealistically low UL for vitamin D. This low UL is itself harmful. The low UL has been, and continues to be, the major hindrance to solving the problem of vitamin D insufficiency in adults.

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