

Critique of the Considerations for Establishing Tolerable Upper Intake Levels for Vitamin D

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Abbreviations used in this manuscript:

AI, adequate intake; RDA, recommended dietary allowance; UL, tolerable upper limit for a nutrient; UF, uncertainty factor that is divided into the no observed adverse effect level to obtain the UL; IOM, Institute of Medicine North America; EVM, Expert Group on Vitamins and Minerals, Great Britain; EC, European Commission Health & Consumer Protection Directorate-General; 25(OH)D, 25-hydroxyvitamin D.

ABSTRACT

Vitamin D is the best example of why care should be taken to avoid excessive intake of vitamin supplements. This creates major difficulties in establishing what is safe and what is excessive. The tolerable upper intake level (UL) for vitamin D is officially 25 mcg (2000 IU)/day or less, but sun exposure can safely provide an adult with vitamin D equivalent of 250 mcg/day. Oral intake of at least 250 mcg/day does not cause harm. The incremental consumption of 1 mcg/day of vitamin D₃ raises serum 25-hydroxyvitamin D (25(OH)D) by about 2.5 nmol/L (1 ng/mL). Published reports show that toxicity may occur with 25(OH)D concentrations beyond 700 nmol/L (280 ng/mL). Older adults are now advised to sustain 25(OH)D concentrations over 75 nmol/L. Together, the preceding numbers permit simple calculations to show that vitamin D₃ intake at the UL raises 25(OH)D by about 50 nmol/L, and that this is far more desirable than harmful. The past decade has produced separate North American, European, and British advice about the adult UL for vitamin D. Despite similar well-defined models for risk assessment and for deriving UL values, each successive report has failed to raise the UL in response to new evidence of no adverse effect at higher doses. Instead,

the uncertainty factor (UF) has been going up, a move contrary to the purpose of the UF. Inappropriately low UL recommendations have hindered objective clinical research into vitamin D nutrition, and they have restricted the amount of vitamin D in multivitamins and foods to doses too low to ensure desirable 25(OH)D concentrations for the public.

Introduction

The following discussion addresses specifically the upper limit intake of vitamin D, because many considerations are unique for this nutrient. Unlike the slow, subtle effects of most forms of nutrient 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). All of this places vitamin D in the ominous position of being the best example of why care should be taken to avoid excessive intake of vitamins. Safety is of course an important issue; however, few who address this issue state specifically what is meant by an "excessive intake" of vitamin D.

The Vague Terminology of Vitamin D Safety.

The Institute of Medicine, through a Canadian/United States Subcommittee on Upper Reference Levels of Nutrients (IOM) and the European Commission's Health & Consumer Protection Directorate-General (EC) define the safety limit as a tolerable upper-intake level (6, 7). The British Expert Group on Vitamins and Minerals (EVM) may specify a "safe upper limit" but when it comes to vitamin D, the EVM fails to provide a value (8). For the sake of simplicity, I abbreviate all of the safety levels or limits generically as the UL.

The UL is important because its purpose is to ensure public safety. However, one might question whether the ULs established for vitamin D fulfill this purpose at all. Over the past decade, "excessive intake" of vitamin D has come to be defined for most people by the UL; however, this has never been the intent of the UL! It is very unfortunate that the definition of the UL is ambiguous, based more on what it is *not*, than what it is. The IOM states that "intakes below the UL are not likely to pose risks of adverse effects in healthy people" (6, 9). The definition in Europe is similar, but in Britain the EVM definition is more straightforward: "SULs (safe upper limits) 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) However, the EVM does not define a safe level for vitamin D, and has offered a "guidance level" instead. For vitamin D, that is explained like a generic UL, where the intake of 25 mcg (1000 IU)/day "would not be expected to cause adverse effects in the general population." (8).

The European Commission (EC) used definitions for safety, and evaluation procedures like those of the North American IOM, but it focused even more on the enlightened approach of targeting serum 25(OH)D concentrations rather than the dose of vitamin D₃ per se. From the 100 mcg/d dose of vitamin D₃ that produced

25(OH)D levels as high as 150 nmol/L (10, 11), it applied an uncertainty factor (UF) of 2, and the EC ended up with a UL of 50 mcg/day (7). All of the 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 (non-medically supervised), apparently healthy individuals" (9). Whether intended or not, at least five interest groups are affected by the UL (Table 1). Each group draws different implications from the UL for vitamin D. Like it or not, boards that specify a UL should address the implications to stakeholders affected by it. My own interest relates to research, and the problem there is that the UL for vitamin D determines the allowable dosage to be used in clinical studies. There are several examples of this (12-14). In theory, the UL is based upon knowledge gained through research. However, there is something terribly wrong when the UL has determined, and continues to determine, dosages used in the very research the UL is supposed to be based upon.

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 no-observed-adverse-effect-level (NOAEL) in this figure represents the highest dose of supplement published that has not been associated with toxicity. The UL is obtained by adjusting the NOAEL downward by dividing by an uncertainty factor (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). Table 2 summarizes the considerations for safe upper limits of nutrients as outlined by the relevant bodies (6-8), and which have been further explained by Walter (15).

Unrealistic hypothetical curves for risk of vitamin D deficiency and excess.

The top panel of Figure 1 shows the fundamental assumption that for all nutrients, there is a wide gap between risk of nutrient inadequacy and the risk of nutrient excess. The flat section of the graph is entirely hypothetical, and it 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 (7, 8). A narrow gap like what is represented by the middle panel of Figure 1, would force committees to be realistic, and to balance risks and benefits.

All committees that have addressed the issue of vitamin D safety have ignored the possibility that a narrower minimum risk zone, like what is hypothetically represented by the middle panel of Figure 1 might be appropriate. The situation we seem to be facing at the moment with respect to vitamin D is a UL of 50 mcg/day, and evidence that the total daily adult requirement is 100 mcg/day (16).

Failure to define what is a physiologic “intake” of vitamin D?

The harm caused by establishing a UL in the absence of a Recommended Dietary Allowance (RDA) is that the UL impedes objective progress for clinical nutrition research across the range of physiologic vitamin D supplies. If vitamin D intakes higher than the current UL of 25 – 50 mcg/day have health benefits relevant to establishing an RDA, the evidence needed beyond the UL becomes extremely difficult to uncover through research involving vitamin D supplementation.

For vitamin D, the nutritional value is not straightforward. Very few foods naturally contain vitamin D. The British EVM document never does explain what it means by a "nutritional value" for any nutrient, let alone vitamin D (8). In North America the Adequate Intake (AI) is not an objective substitute for a nutritional value. By definition, the AI is simply a suggestion made in the absence of suitable evidence of requirement (6, 17). Consequently, unless an RDA is established from an Estimated Average Requirement (EAR) which is based on the findings of research designed for the purpose of setting an RDA, there should be no valid justification for a UL for a nutrient either. The sort of relationship represented by the middle panel of Figure 1 is always possible. For vitamin D, an objectively characterized RDA for adults may well turn out to be similar per kilogram to what has long been recommended for infants – equivalent to more than 50 mcg/day for adults, and more than any UL for vitamin D. An argument for raising the RDA for elderly adults was presented in this symposium (16).

There is evidence that doses of vitamin D₃ of at least 50 mcg/d (2000 IU/day) suppress PTH and improve well-being during the winter better than the highest current AI (18). They can produce a substantial increase in bone density in the elderly (19), and a slowdown in the rate of rise of prostate specific antigen in men with recurrence of prostate cancer (12). Cross-sectionally, bone mineral density in men and women rises progressively with 25(OH)D concentrations beyond 100 nmol/L (20, 21). In Great Britain, risk of breast cancer is much less for women with 25(OH)D levels exceeding 100 nmol/L than for those with concentrations less than 50 nmol/L (22). To ensure that all sun-deprived elderly achieve 25(OH)D levels of at least 75 nmol/L (23), they will all have to consume approximately 100 mcg/d of vitamin D (10). The British guidance level for vitamin D restricts intake to 25 mcg/d or less (8), and this creates the impossible situation in which 50% of older adults who consume the UL for vitamin D in Great Britain fail to meet the current osteoporosis-preventing standard of 75 nmol/L (10, 23). If the goal were to ensure that 25(OH)D levels for all people exceed 75 nmol/L, then the reality for vitamin D may turn out to be what is represented by the middle or the bottom panels of Figure 1.

The “nutritional value” for vitamin D should be defined as an amount of vitamin D equivalent to what an adult can acquire through exposure of full skin surface to summer sunshine. That is, a physiologic intake of vitamin D for an adult can range to 250 mcg/day (24-26).

For every other nutrient, "physiologic" is an amount that can be acquired by eating normal diet. What makes vitamin D different is that supplementation is intended to compensate for a deficiency of sunshine (18, 27). It must also be kept

in mind that "pharmacologic" in the context of vitamin D is not necessarily something "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 high-dose vitamin D have been in the form of vitamin D₂, a compound that is not naturally present in foods or in primate circulation (28). The biology of ergocalciferol (vitamin D₂) is so different from that of vitamin D₃, that if vitamin D₂ were discovered today, its use as a nutritional supplement would probably not be permitted (29-31). Therefore, food-related deliberations about the safety of vitamin D supplementation should focus specifically on evidence pertaining to vitamin D₃ as the natural, physiologic product.

A low UL for vitamin D may be increasing the risk of skin cancer.

The risk of skin cancer is considered so serious by the dermatology profession that the mere publication of a book, *The UV Advantage* (32), in which sun exposure is suggested as a way to acquire a meaningful amount of vitamin D, has resulted in dismissal of its author, Michael Holick, from an academic department of dermatology (33). The strongest case to be made for the health effects of sun tanning is that ultraviolet light is the most abundant source of vitamin D readily available to adults (34). The low UL for vitamin D is driving people to the tanning industry as the only feasible way for them to acquire a meaningful supply of this nutrient through much of the year. Dermatologists are adamant that this is harmful to human health, and the American Academy of Dermatology is now pressing for an upward revision of dietary guidelines for vitamin D (35).

UL Considerations: Hazard identification.

Hypercalcemia is the classic criterion for vitamin D excess. Hypercalciuria can occur at vitamin D doses lower than those that cause hypercalcemia (36). The issue of what is causing 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 (37). Furthermore, according to epidemiologic evidence there is no relationship between vitamin D intakes and incidence of hypercalciuria (38).

The mechanisms by which vitamin D is toxic at the molecular level have been reviewed (39). 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 approximately 4700 nmol/L (40). 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. Lastly, vitamin D₂ generates metabolites for which there is no physiologic, vitamin D₃, equivalent. The unique vitamin D₂ metabolites may also account for harmful effects of excessive intakes of this unnatural compound (41).

The quality and completeness of the data that support the current NOAEL and the LOAEL are highly questionable. Official reports tend to focus on the studies by Narang, and by Johnson (42, 43) to support the risk of harm at intakes around the current UL. The problems with the study by Narang have been thoroughly dealt with elsewhere (10, 44). The report of Johnson in its abstract – not in its result section – mentions that 2 of 63 vitamin D-supplemented patients developed hypercalcemia, but none of the 40 placebo patients developed hypercalcemia (43). Although the difference in incidence of hypercalcemia is certainly not significant ($p=0.52$), that publication is the main justification for British conservatism about the vitamin D UL (8). Another paper highlighted by the EVM is by Honkanen et al, who supplemented free living adults and institutionalized elderly with 45 mcg (1800 IU)/day vitamin D (45). 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 three subjects in their study who developed hypercalcemia were in the placebo group! This aspect of the Honkanen report was overlooked by the EVM (8). If one combines the two hypercalcemic patients with vitamin D from the Johnson study with the three hypercalcemic patients in the placebo group from the Honkanen study, it becomes clear that consumption of vitamin D in the vicinity of 50 mcg/day (2000 IU/day) has no ill effect whatsoever. The traditional definition of hypercalcemia is a serum or plasma calcium higher than the 97.5th percentile of levels in a normal population. Because both Johnson et al and Honkanen et al involved more than 100 patients, the number of subjects whose calcium became "hypercalcemic" 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, 46), and at 250 mcg/d (47, 48).

Probably the most helpful publications from a public-health perspective about the risks of vitamin D intake are the reports about the case of a home-delivery dairy serving 11,000 households in Boston, which over-fortified milk with highly variable amounts of vitamin D (49, 50). Based on the dairy's purchase records of vitamin D, the average quart of milk contained 300 mcg (12,000 IU)/quart between the years 1985 to 1991. However, the error due to the bad dispensing equipment for vitamin D ranged to doses as high as 6000 mcg/quart (normal should be 10 mcg/quart). Blank et al reported that there were 56 cases of suspected or confirmed vitamin D intoxication. 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, one should have expected far more cases of hypercalcemia.

UL Considerations: Dose-response relationships.

Human studies. Several reports that amount to 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 doses of vitamin D₂ of at least 40,000 IU (1000 mcg)/day for several months (24). Patients given regular bolus doses of vitamin D₃ (7500 mcg (300,000 IU)/week) can develop hypercalcemia (51). The hypercalcemia was associated with 25(OH)D levels greater than 1000 nmol/L. However, patients have been reported with hypercalcemia having 25(OH)D levels as low as 355 nmol/L (52).

Heaney et al. (48) 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 about 1.0 nmol/L when 25(OH)D levels are low, but this increment per mcg/day declines as the 25(OH)D increases beyond 100 nmol/L (30).

Animal Studies. The most complete dose-response relationship published is that of Shepard and DeLuca (53). They gave groups of rats 10-fold increments in vitamin D₃ dose. The highest dose that did not produce hypercalcemia was 65 nmol/day per rat, this works out to 25 mcg (1000 IU) per rat. If we assume that they used relatively large rats, this becomes 50 mcg (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 in the order of 250 mcg (10,000 IU)/day. By the same process, the study of Shepard and DeLuca suggest that the adult human LOAEL may be in the order of ten times that (53).

High-vitamin D dose studies have recently been reported for Great-Dane dogs. Nineteen weeks of supplementation at 1350 micrograms/kilogram did not change serum calcium levels (54). 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, but I acknowledge the dose is far too high to be plausible in terms of safety for humans.

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 1990's did address the issue vitamin D safety. Table 3 summarizes the progression of statements relating to safe and toxic vitamin D intakes. The first allusion to 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/day) may be a limit for infants (55). Because of a lack of information, the same value was later extended to adults (56). That value, 50 mcg (2000 IU)/day, has remained the focus of vitamin D safety committees ever since. Despite the principle that the UL should adjust for uncertainty and evidence, none of the reports about vitamin D safety in recent years appear to have changed the limit first mentioned in 1964.

For past 40 years, the adult safety limits for vitamin D, be they guidance levels or UL values, have remained in the range of 25-50 mcg/day (6-8, 57). In theory, the UF should become smaller as evidence accumulates. However, from

Table 3 it is evident that instead of raising the UL for vitamin D to follow data showing that higher intakes are safe, the UL has remained the same, and the UF has been going up instead.

The appropriate context for the suitability of vitamin D intakes is the effect of sunshine per se. All current reports relating to the UL for vitamin D state that the effect of sunshine makes the analysis confusing. However, all reports acknowledge that sunshine exposure is safe in the context of the amount of vitamin D it generates (6-8). The problem of the combined effect of abundant sunshine with greater vitamin D supplementation becomes quite simple if we focus on serum or plasma 25(OH)D per se. We know very well how much oral vitamin D is required to raise serum 25(OH)D to match the effects of sunshine. Full-body sun exposure is the equivalent of consuming between 250-500 micrograms of vitamin D₃ (24, 25). Casual sun exposure of American outdoor workers can be equivalent to the consumption of about 100 mcg/day of vitamin D₃ (26). If one considers that the human species was effectively designed by evolution to live with skin nearly totally exposed to tropical sunshine, it makes sense that sun-equivalent doses of vitamin D₃ cannot be associated with harm – these amounts are natural and perhaps even optimal for our primate biology (18).

The concern that harm may result from the combination of a high intake of vitamin D along with abundant sun exposure must be addressed. Based upon the long history of vitamin D use in doses above 1000 mcg/d (40,000 IU/day), it is reasonable to infer that the LOAEL for adults is near that value. From experience with patients intoxicated with vitamin D₃, we know that it requires 25(OH)D levels of more than 700 nmol/liter to cause an undesirable change calcium homeostasis (1, 2, 4, 24, 50).

There are rare individuals, such as those with sarcoidosis or tuberculosis who should avoid both sunshine and vitamin D (58). However, what should be balanced against this is the possibility that the incidence of these diseases may be higher because of prevailing vitamin D insufficiency. One should ask whether the up-regulation of 1-hydroxylase within these tissues represents a form of vitamin D hunger (59), and that with chronic up-regulation of 1-hydroxylase, some cells lose the ability to down-regulate 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, 60). However, recent work has shown that vitamin D supplementation of patients with primary hyperparathyroidism is noncalcemic, and that it suppresses PTH secretion and bone turnover (61).

Effect of Committee psychology on the uncertainty factor.

Table 3 reveals what 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 that as a move in the direction of greater danger. The path of least resistance is to avoid a change to the UL. This becomes very easy for a group to accept because the guidelines that UL

committees must follow ignore the possibility that a low UL might be a problem in itself (Figure 1, top panel). 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) The psychological barrier and the evidence of Table 3 show that committees addressing the safety of vitamin D adapt to new knowledge that higher doses are safe by raising the uncertainty factor instead of raising the UL. For vitamin D, this has resulted in an unrealistically low UL. This is harmful in itself. The low UL has been, and continues to be the major hindrance to solving the problem of vitamin D insufficiency in adults.

Table 1. Implications of the UL for the interest groups affected by it.

Medical and Health Advisors, and the General public. The UL defines what the public can be advised to take without prescription. It specifies the point where pharmacists advise customers that vitamin D is toxic.

Mainstream supplement industry. The UL defines what industry can provide to the general public without risk of prosecution. Mainstream brands of vitamin supplement offer the public a dose of vitamin D that is no more than half the UL.

Legal profession. The UL defines the point beyond which lawyers may sue companies and health advisors for harm (justified or not) because of excessive vitamin D.

Clinical-nutrition researchers. Beyond the UL, it becomes exceedingly difficult to obtain support from research funding agencies. Grant review panels do not consider it appropriate to fund studies beyond the UL because this is not seen as something relevant to "nutrition". Hence, the UL plays a powerful role in the dosage used for nutrition research.

Research Ethics Committees. They mandate additional monitoring that limits enrollment and increases cost of clinical studies at doses higher than the UL. Consequence: The UL defines and limits the dose of vitamin D that is feasible for clinical research.

Table 2. Process for establishing the safe upper limits for nutrients (6-8, 15, 57).

1. **Hazard identification:** 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 issues are 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. **Characterize Dose–response** between nutrient intake and adverse effect.
 - a) Human data are preferable, but animal data 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 thus establish the UF for extrapolating the observed data 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. (General observation : estimated NOAELs are about 1/3rd the LOAEL).

Table 3. Historic review of specific statements about toxic and tolerable vitamin D intakes for adults.

Report Year (Citation)	mcg/day	mcg/day	mcg/day	mcg/day	Uncertainty Factor (NOAEL / UL)
	mcg/day	LOAEL	NOAEL	UL	
IOM 1958 (62)		no mention of safety.			none
IOM 1964 (55)	(mcg/day)	1250-3750 a			none
IOM 1968 (56)	(mcg/day)		50-75 b		none
IOM 1997 (6)	(mcg/day)	96	60	50	1.2
EC 2002 (7)	(mcg/day)		100	50	2
EVM 2003 (8)	(mcg/day)		100	25	4 c

Footnotes:

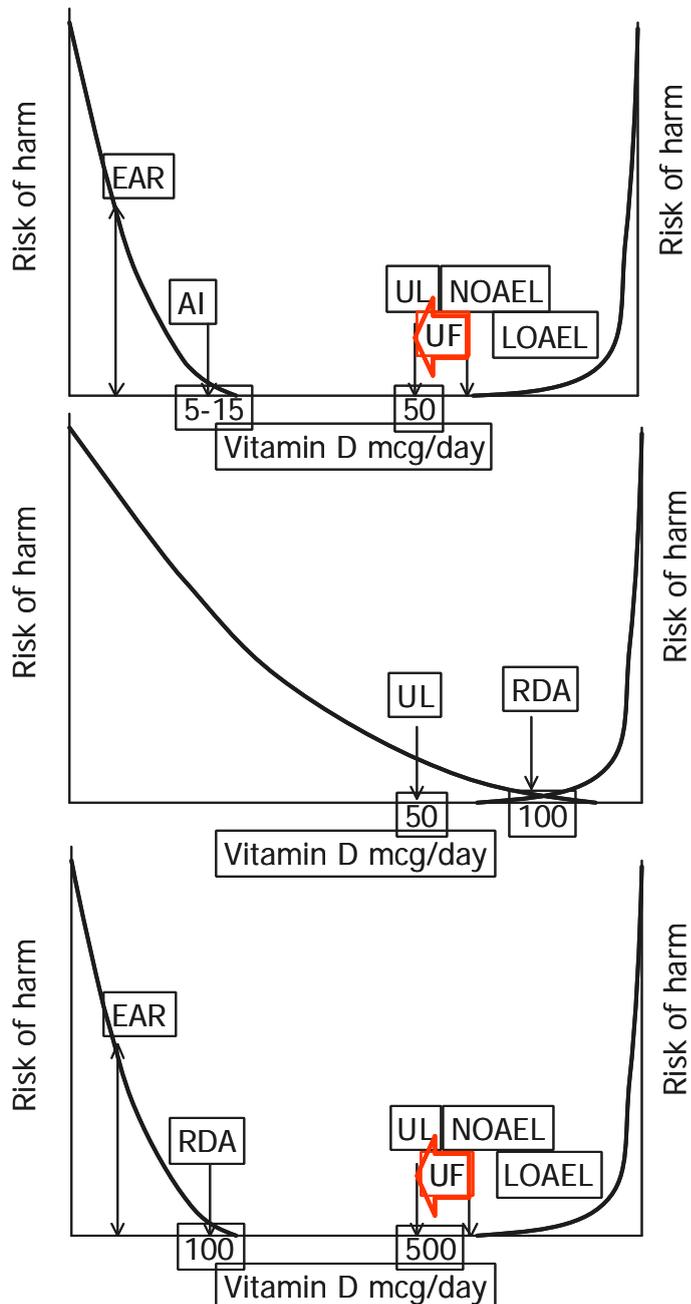
a Adjusted to 50 kg body wt, according to the statement "Excessive quantities of vitamin D (of the order of 1,000 to 3,000 IU/kg/day) are toxic" (55)

b "There is no evidence that intakes in the order of 2000-3000 IU/day produce hypercalcemia beyond infancy" (56) – the historic precedent in North America that 50 mcg/d (2000 IU/d) may be a safe upper limit.

c This is a "guidance level", not quite a UL. Although the British EVM group would not specify an uncertainty factor for vitamin D (pg 143 of its report) (8), the value, 4, above, is the de-facto uncertainty factor. This is because 100 mcg/day was the highest dose stated as safe, followed by the statement, "a level of 0.025 mg/day 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 mention of 2 hypercalcemic subjects in the vitamin D group of Johnson et al (43), but they overlooked the 3 hypercalcemic subjects in the placebo-group of Honkanen et al (45). There is no evidence that at 50 mcg/d causes hypercalcemia at a higher rate. This lack of evidence now extends to 275 mcg/d (48).

Figure 1. Traditional representation of nutrition terms relevant to vitamin D (Top).

The abbreviations represented are the Estimated Average Requirement (EAR) for vitamin D, the Adequate Intake (AI); the Upper Level (UL), calculated by dividing the no-observed-adverse-effect-level (NOAEL) by an uncertainty factor (UF); the dose of long-term vitamin D supplementation that produced the lowest-observed-adverse-level (LOAEL) is also represented. The middle panel represents a different set of relationships for deficiency and excess. The middle graph illustrates a hypothetical situation (but it is implied by combining the current UL with some of the recent evidence of adult requirements (16)). This implies that some healthy adults require vitamin D in an amount that is 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 such a scenario has been explicitly ignored by all reviews of vitamin D safety (6-8, 57). The bottom panel represents what the author proposes may be the reality for vitamin D in the near future, based on an RDA that reflects the vitamin D supply from physiologic sun exposure of adults, and data on dose tolerability.



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