

## **Vitamin D**

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### *Function*

Vitamin D is required in quantities smaller than for any other fat-soluble vitamin. Though it can be synthesized in the body with sufficient exposure to sunlight—or other ultraviolet (UV) light source—the preformed vitamin can be obtained from a limited number of foods or from supplements. No extra vitamin D is required when skin exposure to ultraviolet light is ample; but without such exposure, a person is completely dependent on ingested vitamin D. Thus, vitamin D has been described as a sunshine-dependent hormone. The UV component of sunlight converts internally produced 7-dehydrocholesterol to cholecalciferol (Holick 1999).

The major function of vitamin D is the regulation of calcium metabolism through activated forms of vitamin D<sub>2</sub> (ergocalciferol) and vitamin D<sub>3</sub> (cholecalciferol). Most vitamin D dietary supplements contain vitamin D<sub>3</sub>. Some dietary vitamin D<sub>2</sub> comes from plants, but the largest contribution to dietary intake of vitamin D is the vitamin D<sub>3</sub> in fish liver oils, eggs, milk, and liver. Milk is commonly fortified with 10 µg (400 IU) of vitamin D<sub>3</sub> per quart.

Cholecalciferol is present in the plasma as 25-hydroxycholecalciferol, which is metabolized to produce the metabolically active hormone calcitriol (1 $\alpha$ ,25-dihydroxycholecalciferol). This hormone regulates intestinal absorption and the plasma concentration of calcium. As calcitriol, vitamin D is fundamentally involved in the formation of bone, and its deficiency can lead to rickets in children or osteoporotic changes in adults. Although adequate UV light exposure can provide sufficient vitamin D, many elderly persons have limited sunlight exposure, inadequate dietary sources, and decreased ability to activate vitamin D, making them susceptible to vitamin D deficiency (Gloth et al. 1995; Holick 1999). Thus, the nutritional need for dietary vitamin D depends on the biosynthesis in the skin, which in turn is influenced by time of exposure to sunlight, season (sun intensity and clothing), latitude, skin pigmentation, and use of sunscreens.

### **Safety Evidence**

Formation of vitamin D in the skin is inhibited once dietary vitamin D intakes are sufficient and blood levels of the hydroxylated forms are high. Therefore, excess exposure to sunlight does not lead to vitamin D toxicity (Holick 1999).

Dietary vitamin D can, however, produce toxic effects when consumed in large quantities over an extended period of time. Studies have shown that subjects with abnormally high levels of vitamin D intake can suffer from a wide range of signs and symptoms, from dehydration to permanent mineral deposits in soft tissues, including muscle, heart, kidney, and cartilage. Continued intake of toxic levels can have severe and persistent adverse consequences. The widespread occurrence of vitamin D overdose in British children just after World War II, caused by consumption of excessively fortified milk, led health professionals to be extremely conservative in estimating safe levels for vitamin D.

Prolonged intake of excess vitamin D may lead to predictable increases in plasma 25-hydroxy vitamin D concentrations (Food and Nutrition Board 1997), and the increase is directly proportional to the vitamin D dose (Barger-Lux et al. 1998). Treatment with vitamin D or 25-hydroxy vitamin D does not generally increase the serum concentrations of the active metabolite (calcitriol,  $1\alpha,25$ -dihydroxycholecalciferol, or 1,25-dihydroxy vitamin D) (Barger-Lux et al. 1998). Nonetheless, excess vitamin D can have toxic effects, perhaps because of the increase in blood concentration of 25-hydroxy vitamin D, a form that can overstimulate intestinal absorption of calcium and cause excessive calcium mobilization from bone and hypercalcemia (Norman 1996; Holick 1999).

The amount of daily vitamin D ingestion needed to produce adverse effects varies widely. In most adults, daily intake in excess of 1.25 mg (50,000 IU) is needed to produce toxicity (Miller and Hayes 1982; Food and Nutrition Board 1997), but much less may cause adverse effects in some persons. In certain diseases such as sarcoidosis, mycobacterium infections such as tuberculosis, or idiopathic hypercalcemia, toxicity can occur at levels of vitamin D intake only somewhat above normal (greater than 25  $\mu$ g, or 1,000 IU per day). A causal relationship between excess vitamin D intake and idiopathic hypercalcemia is unlikely, although persons with idiopathic hypercalcemia may be subject to adverse effects of vitamin D at lower intakes than may be comfortably tolerated by healthy individuals (SCOGS 1978).

One study has found that in children of unreported body weight (probably between 10 and 30 kg), the amount of dietary vitamin D causing adverse effects may be as low as 50 to 100  $\mu$ g (2,000 to 4,000 IU) per day. In full-term infants, adverse effects are reported to occur with intakes as low as 45  $\mu$ g (1,800 IU) per day (Chesney 1989), but no adverse effects occurred in a six-month study of infants given 1,600 IU per day (Fomon et al. 1966). No adverse effects were observed in a clinical trial involving 3,000 elderly women given 20  $\mu$ g (800 IU) per day for eighteen months (Chapuy et al. 1992).

Numerous reports confirm a variety of adverse effects at very high intakes when vitamin D is used as a drug, whether administered in activated forms or

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parenterally (Boulard et al. 1994; Oymak et al. 1994; Nanji 1985; Schwartzman and Franck 1987; Goldman and Wheeler 1987; Matsukawa et al. 1995; Allen and Shah 1992). These circumstances do not relate to the usual oral intakes of vitamin D from foods or dietary supplements, and most reports provide no useful information about the safety of dietary sources of vitamin D.

## **Published Official Reviews of Vitamin D Safety**

The FNB has established a UL of 50 µg vitamin D, based on a NOAEL of 60 µg (from the data of Narang et al. 1984) and application of an uncertainty factor of 1.2 (Food and Nutrition Board 1997).

The EC SCF established a UL of 50 µg vitamin D, based on a NOAEL of 100 µg (from Vieth et al. 2001) and application of an uncertainty factor of 2 (Scientific Committee on Food 2002). The factor of 2 was intended to account for inter-individual variation.

The UK EVM did not find the data sufficiently compelling to identify a NOAEL or a LOAEL. Instead, it set a GL at 25 µg, based on studies at 100 µg (Vieth et al. 2001) and at 50 µg (Johnson et al. 1980). Without identification of a NOAEL or a LOAEL or application of any uncertainty factor, UK EVM concluded that long-term use of supplements at 25 µg was “well tolerated” (Expert Group on Vitamins and Minerals 2003).

## **CRN ULS for Vitamin D**

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The extreme and scientifically unjustified conservatism by health professionals in relation to the potential toxicity of vitamin D is rapidly being corrected to an evidence-based assessment, with the resulting conclusion being that amounts much larger than previously thought to be safe are now considered safe for most persons.

The data by Vieth and coworkers (Vieth et al. 2001) indicate that the NOAEL for vitamin D might be as high as 100 µg. Thus, from the available data, the LOAEL is greater than 100 µg per day in relation to its hypercalcemic effects. The FNB and UK EVM estimate vitamin D intakes from all non-supplement sources to be in the range of 9 µg (360 IU) or less. The majority of dietary supplements that include vitamin D contain 10 µg (labeled in the U.S. as 400 IU) or less. There are no reports of adverse effects at this level of intake.

The CRN ULS is identified as 60 µg (2,400 IU), based on the absence of adverse effects in a clinical trial (Narang et al. 1984). The FNB identified a NOAEL of 60 µg based on these data, but applied an uncertainty factor of 1.2. CRN considers the database for an intake of 100 µg to be highly supportive of a NOAEL at that

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level, but perhaps not yet replete enough to warrant setting the NOAEL that high. However, the data from Vieth and coworkers strongly reduce any uncertainty about the safety at a 60 µg intake.

CRN, having confidence in the safety of the 60 µg intake level provided by the data related to 100 µg intake, does not consider a NOAEL of 60 µg to need adjustment by application of an uncertainty factor (meaning that, implicitly, an uncertainty factor of 1.0 is applied). Thus, CRN sets the ULS at 60 µg (2,400 IU), based on the 60 µg clinical trial data and a non-supplement intake of not more than 9 µg.

### **Comparison of Safety Values for Vitamin D**

<b>CRN ULS (60 µg , 1)</b>	60 µg (2,400 IU)
<b>US FNB UL (60 µg , 1.2)</b>	50 µg
<b>EC SCF UL</b>	50 µg
<b>EC supplement maximum</b>	Not established (as of May 2004)
<b>UK EVM GL, supplement</b>	25 µg

### *References*

Allen SH, Shah JH. Calcinosis and metastatic calcification due to vitamin D intoxication. *Hormone Research* 1992; 37:68-77.

Barger-Lux MJ, Heaney RP, Dowell S, Chen TC, Holick MF. Vitamin D and its major metabolites: Serum levels after graded oral dosing in healthy men. *Osteoporosis Int* 1998; 8:222-230.

Boulard JC, Hanslik T, Alterescu R, Baglin A. Hypercalcémie symptomatique après association vitamine D diurétiques thiazidiques: 2 observations chez des femmes dosés [letter]. *La Presse Medicale* 1994; 22:96.

Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, Delmas PD, Meunier PJ. Vitamin D<sub>3</sub> and calcium to prevent hip fractures in elderly women. *N Engl J Med* 1992; 327:1637-1642.

Chesney RW. Vitamin D: Can an upper limit be defined? *J Nutr* 1989; 119:1825-1828.

Expert Group on Vitamins and Minerals. Safe upper levels for vitamins and minerals, Food Standards Agency, United Kingdom, 2003.

Fomon SJ, Younoszal MK, Thomas LN. Influence of vitamin D on linear growth of normal full-term infants. *J Nutr* 1966; 88:345-350.

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Food and Nutrition Board. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: National Academy Press, 1997.

Gloth FM, Gundberg CM, Hollis BW, Haddad JG, Tobin JD. Vitamin D deficiency in homebound elderly persons. *JAMA* 1995; 274:1638-1646.

Goldman JM, Wheeler MF. Vitamin D-induced hypercalcemia [letter]. *Am J Med* 1987; 82:1277.

Holick MF. Vitamin D. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern nutrition in health and disease*, 9th ed. Philadelphia: Williams & Wilkins, 1999; 329-345.

Johnson KR, Jobber J, Stonawski BJ. Prophylactic vitamin D in the elderly. *Age and Aging* 1980; 9:121-127.

Matsukawa Y, Ikeda E, Hayama T, Nishinaita S, Sawada S, Horie T. Ectopic calcinosis possibly due to lot (OH) vitamin D<sub>3</sub> in a patient with systemic lupus erythematosus. *Clin Exper Rheum* 1995; 13:91-94.

Miller DR, Hayes KC. Vitamin excess and toxicity. In: Hathcock JN, ed. *Nutritional toxicology*, vol. 1. New York: Academic Press, 1982; 81-133.

Nanji AA. Symptomatic hypercalcaemia precipitated by magnesium therapy. *Postgraduate Med J* 1985; 61:47-48.

Narang NK, Gupta RC, Jain NK. Role of vitamin D in pulmonary tuberculosis. *J Assoc of Physicians of India* 1984; 32:185-188.

Norman AW. Vitamin D. In: *Present knowledge of nutrition*, 7th ed. Washington, DC: ILSI Press, 1996; 120-129.

Oymak O, Ak-polat T, Arik N, Yasavul C, Turgan Q, Caglar S. Hyperammonemic encephalopathy due to vitamin D induced hypercalcemia in a uremic patient [letter]. *Nephron* 1994; 66:369.

Schwartzman MS, Franck WA. Vitamin D toxicity complicating the treatment of senile, postmenopausal, and glucocorticoid-induced osteoporosis. *Am J Med* 1987; 82:224-230.

Scientific Committee on Food. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin E. European Commission, SCF/CS/NUT/UPPERLEV/31 Final, Brussels, 2002.

SCOGS: Select Committee on GRAS Substances, Life Sciences Research Office (LSRO). Evaluation of the health aspects of vitamin D<sub>2</sub> and vitamin D<sub>3</sub> as food ingredients. Washington, DC. Federation of American Societies for Experimental Biology, 1978.

Vieth R, Chan P, MacFarlane, GD. Efficacy and safety of vitamin D<sub>3</sub> intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr* 2001; 73:288-294.