



Dietary Supplement Fact Sheet

Vitamin D

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Introduction

Vitamin D is a fat-soluble vitamin that is naturally present in very few foods, added to others, and available as a dietary supplement. It is also produced endogenously when ultraviolet rays from sunlight strike the skin and trigger vitamin D synthesis [1-3]. Vitamin D obtained from sun exposure, food, and supplements is biologically inert and must undergo two hydroxylations in the body for activation. The first occurs in the liver and converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. The second occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25(OH)₂D], also known as calcitriol [4].

Vitamin D is essential for promoting calcium absorption in the gut and maintaining adequate serum calcium and phosphate concentrations to enable normal mineralization of bone and prevent hypocalcemic tetany. It is also needed for bone growth and bone remodeling by osteoblasts and osteoclasts [4-6]. Without sufficient vitamin D, bones can become thin, brittle, or misshapen. Vitamin D sufficiency prevents rickets in children and osteomalacia in adults [3,7,8]. Together with calcium, vitamin D also helps protect older adults from osteoporosis.

Vitamin D has other roles in human health, including modulation of neuromuscular and immune function and reduction of inflammation. Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D [4,6,9,10]. Many laboratory-cultured human cells have vitamin D receptors and some convert 25(OH)D to 1,25(OH)₂D [11]. It remains to be determined whether cells with vitamin D receptors in the intact human carry out this conversion.

Serum concentration of 25(OH)D is the best indicator of vitamin D status. It reflects vitamin D produced cutaneously and that obtained from food and supplements [5] and has a fairly long circulating half-life of 15 days [15]. However, serum 25(OH)D levels do not indicate the amount of vitamin D stored in other body tissues. Circulating 1,25(OH)₂D is generally not a good indicator of vitamin D status because it has a short half-life of 15 hours and serum concentrations are closely regulated by parathyroid hormone, calcium, and phosphate [15]. Levels of 1,25(OH)₂D do not typically decrease until vitamin D deficiency is severe [6,11].

There is considerable discussion of the serum concentrations of 25(OH)D associated with deficiency (e.g., rickets), adequacy for bone health, and optimal overall health (Table 1). A concentration of <20 nanograms per milliliter (ng/mL) (or <50 nanomoles per liter [nmol/L]) is generally considered inadequate.

Table 1: Serum 25-Hydroxyvitamin D [25(OH)D] Concentrations and Health*

ng/mL**	nmol/L**	Health status
<11	<27.5	Associated with vitamin D deficiency and rickets in infants and young children [5].
<10-15	<25-37.5	Generally considered inadequate for bone and overall health in healthy individuals [5,13].
≥30	≥75	Proposed by some as desirable for overall health and disease prevention, although a recent government-sponsored expert panel concluded that insufficient data are available to support these higher levels [13,14].
Consistently >200	Consistently >500	Considered potentially toxic, leading to hypercalcemia and hyperphosphatemia, although human data are limited. In an animal model, concentrations ≤400 ng/mL (≤1,000 nmol/L) demonstrated no toxicity [15,16].

* Serum concentrations of 25(OH)D are reported in both nanograms per milliliter (ng/mL) and nanomoles per liter (nmol/L).

** 1 ng/mL = 2.5 nmol/L.

Reference Intakes

Intake reference values for vitamin D and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine of The National Academies (formerly National Academy of Sciences) [5]. DRI is the general term for a set of reference values used to plan and assess nutrient intakes of healthy people. These values, which vary by age and gender [5], include:

- Recommended Dietary Allowance (RDA): average daily level of intake sufficient to meet the nutrient requirements of nearly all (97-98%) healthy people.
- Adequate Intake (AI): established when evidence is insufficient to develop an RDA and is set at a level assumed to ensure nutritional adequacy.
- Tolerable Upper Intake Level (UL): maximum daily intake unlikely to cause adverse health effects [5].

The FNB established an AI for vitamin D that represents a daily intake that is sufficient to maintain bone health and normal calcium metabolism in healthy people. AIs for vitamin D are listed in both micrograms (mcg) and International Units (IUs); the biological activity of 1 mcg is equal to 40 IU (Table 2). The AIs for vitamin D are based on the assumption that the vitamin is not synthesized by exposure to sunlight [5].

Table 2: Adequate Intakes (AIs) for Vitamin D [5]

Age	Children	Men	Women	Pregnancy	Lactation
Birth to 13 years	5 mcg (200 IU)				
14-18 years		5 mcg (200 IU)	5 mcg (200 IU)	5 mcg (200 IU)	5 mcg (200 IU)
19-50 years		5 mcg (200 IU)	5 mcg (200 IU)	5 mcg (200 IU)	5 mcg (200 IU)
51-70 years		10 mcg (400 IU)	10 mcg (400 IU)		
71+ years		15 mcg (600 IU)	15 mcg (600 IU)		

In 2008, the American Academy of Pediatrics (AAP) issued recommended intakes for vitamin D that exceed those of FNB [18]. The AAP recommendations are based on evidence from more recent clinical trials and the history of safe use of 400 IU/day of vitamin D in pediatric and adolescent populations. AAP recommends that exclusively and partially breastfed infants receive supplements of 400 IU/day of vitamin D shortly after birth and continue to receive these supplements until they are weaned and consume ≥1,000 mL/day of vitamin D-fortified formula or whole milk [18]. (All

formulas sold in the United States provide ≥ 400 IU vitamin D₃ per liter, and the majority of vitamin D-only and multivitamin liquid supplements provide 400 IU per serving.) Similarly, all non-breastfed infants ingesting $< 1,000$ mL/day of vitamin D-fortified formula or milk should receive a vitamin D supplement of 400 IU/day. AAP also recommends that older children and adolescents who do not obtain 400 IU/day through vitamin D-fortified milk and foods should take a 400 IU vitamin D supplement daily [18].

Sources of Vitamin D

Food

Very few foods in nature contain vitamin D. The flesh of fish (such as salmon, tuna, and mackerel) and fish liver oils are among the best sources [5]. Small amounts of vitamin D are found in beef liver, cheese, and egg yolks. Vitamin D in these foods is primarily in the form of vitamin D₃ (cholecalciferol) and its metabolite 25(OH)D₃ [19]. Some mushrooms provide vitamin D₂ (ergocalciferol) in variable amounts [20-22].

Fortified foods provide most of the vitamin D in the American diet [5,22]. For example, almost all of the U.S. milk supply is fortified with 100 IU/cup of vitamin D (25% of the Daily Value or 50% of the AI level for ages 14-50 years). In the 1930s, a milk fortification program was implemented in the United States to combat rickets, then a major public health problem. This program virtually eliminated the disorder at that time [5,14]. Other dairy products made from milk, such as cheese and ice cream, are generally not fortified. Ready-to-eat breakfast cereals often contain added vitamin D, as do some brands of orange juice, yogurt, and margarine. In the United States, foods allowed to be fortified with vitamin D include cereal flours and related products, milk and products made from milk, and calcium-fortified fruit juices and drinks [22]. Maximum levels of added vitamin D are specified by law.

Several food sources of vitamin D are listed in Table 3.

Table 3: Selected Food Sources of Vitamin D [23-25]

Food	IUs per serving*	Percent DV**
Cod liver oil, 1 tablespoon	1,360	340
Salmon, cooked, 3.5 ounces	360	90
Mackerel, cooked, 3.5 ounces	345	90
Tuna fish, canned in oil, 3 ounces	200	50
Sardines, canned in oil, drained, 1.75 ounces	250	70
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	98	25
Margarine, fortified, 1 tablespoon	60	15
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75-1 cup (more heavily fortified cereals might provide more of the DV)	40	10
Egg, 1 whole (vitamin D is found in yolk)	20	6
Liver, beef, cooked, 3.5 ounces	15	4
Cheese, Swiss, 1 ounce	12	4

*IUs = International Units.

**DV = Daily Value. DVs were developed by the U.S. Food and Drug Administration to help consumers compare the nutrient contents of products within the context of a total diet. The DV for vitamin D is 400 IU for adults and children age 4 and older. Food labels, however, are not required to list vitamin D content unless a food has been fortified with this nutrient. Foods providing 20% or more of the DV are considered to be high sources of a nutrient.

The U.S. Department of Agriculture's Nutrient Database Web site, <http://www.nal.usda.gov/fnic/foodcomp/search/> [26], lists the nutrient content of many foods; relatively few have been analyzed for vitamin D content.

Sun exposure

Most people meet their vitamin D needs through exposure to sunlight [6,27]. Ultraviolet (UV) B radiation with a wavelength of 290-315 nanometers penetrates uncovered skin and converts cutaneous 7-dehydrocholesterol to previtamin D₃, which in turn becomes vitamin D₃ [11,27-28]. Season, geographic latitude, time of day, cloud cover, smog, skin melanin content, and sunscreen are among the factors that affect UV radiation exposure and vitamin D synthesis [28]. The UV energy above 42 degrees north latitude (a line approximately between the northern border of California and Boston) is insufficient for cutaneous vitamin D synthesis from November through February [6]; in far northern latitudes, this reduced intensity lasts for up to 6 months. Latitudes below 34 degrees north (a line between Los Angeles and Columbia, South Carolina) allow for cutaneous production of vitamin D throughout the year [14]

Complete cloud cover reduces UV energy by 50%; shade (including that produced by severe pollution) reduces it by 60% [29]. UVB radiation does not penetrate glass, so exposure to sunshine indoors through a window does not produce vitamin D [30]. Sunscreens with a sun protection factor of 8 or more appear to block vitamin D-producing UV rays, although in practice people generally do not apply sufficient amounts, cover all sun-exposed skin, or reapply sunscreen regularly [31]. Skin likely synthesizes some vitamin D even when it is protected by sunscreen as typically applied.

The factors that affect UV radiation exposure and research to date on the amount of sun exposure needed to maintain adequate vitamin D levels make it difficult to provide general guidelines. It has been suggested by some vitamin D researchers, for example, that approximately 5-30 minutes of sun exposure between 10 AM and 3 PM at least twice a week to the face, arms, legs, or back without sunscreen usually lead to sufficient vitamin D synthesis and that the moderate use of commercial tanning beds that emit 2-6% UVB radiation is also effective [11,28]. Individuals with limited sun exposure need to include good sources of vitamin D in their diet or take a supplement.

Despite the importance of the sun to vitamin D synthesis, it is prudent to limit exposure of skin to sunlight [31]. UV radiation is a carcinogen responsible for most of the estimated 1.5 million skin cancers and the 8,000 deaths due to metastatic melanoma that occur annually in the United States [31]. Lifetime cumulative UV damage to skin is also largely responsible for some age-associated dryness and other cosmetic changes. It is not known whether a desirable level of regular sun exposure exists that imposes no (or minimal) risk of skin cancer over time. The American Academy of Dermatology advises that photoprotective measures be taken, including the use of sunscreen, whenever one is exposed to the sun [83].

Dietary supplements

In supplements and fortified foods, vitamin D is available in two forms, D₂ (ergocalciferol) and D₃ (cholecalciferol). Vitamin D₂ is manufactured by the UV irradiation of ergosterol in yeast, and vitamin D₃ is manufactured by the irradiation of 7-dehydrocholesterol from lanolin and the chemical conversion of cholesterol [11]. The two forms have traditionally been regarded as equivalent based on their ability to cure rickets, but evidence has been offered that they are metabolized differently. Vitamin D₃ could be more than three times as effective as vitamin D₂ in raising serum 25(OH)D concentrations and maintaining those levels for a longer time, and its metabolites have superior affinity for vitamin D-binding proteins in plasma [6,32,33]. Because metabolite receptor affinity is not a functional assessment, as the earlier results for the healing of rickets were, further research is needed on the comparative physiological effects of both forms. Many supplements are being reformulated to contain vitamin D₃ instead of vitamin D₂ [33]. Both forms (as well as vitamin D in foods and from cutaneous synthesis) effectively raise serum 25(OH)D levels [6].

Vitamin D Intakes and Status

In 1988-1994, as part of the third National Health and Nutrition Examination Survey (NHANES III), the frequency of use of some vitamin D-containing foods and supplements was examined in 1,546 non-Hispanic African American women and 1,426 non-Hispanic white women of reproductive age (15-49 years) [34]. In both groups, 25(OH)D levels were higher in the fall (after a summer of sun exposure) and when milk or fortified cereals were consumed more than three times per week. The prevalence of serum concentrations of 25(OH)D \leq 15 ng/mL (\leq 37.5 nmol/L) was 10 times greater for the African American women (42.2%) than for the white women (4.2%).

The 2000-2004 NHANES provided the most recent data on the vitamin D nutritional status of the U.S. population [35]. Generally, younger people had higher serum 25(OH)D levels than older people; males had higher levels than females; and non-Hispanic whites had higher levels than Mexican Americans, who in turn had higher levels than non-Hispanic blacks. Depending on the population group, 1-9% had serum 25(OH)D levels $<$ 11 ng/mL ($<$ 27.5 nmol/L), 8-36% had levels

<20 ng/mL (<50 nmol/L), and the majority (50-78%) had levels <30 ng/mL (<75 nmol/L). Among adults in the United Kingdom, nationally representative data collected between 1992 and 2001 show that 5-20% in most age groups on average had serum 25(OH)D levels <10 ng/ml (<25 nmol/L); the prevalence of deficiency was greater (range 20-40%) for older people >65 years of age in residential care homes and among women >85 years. Among all adults, 20-60% had levels \leq 20 ng/ml (\leq 50 nmol/L) and 90% had levels \leq 32 ng/ml (\leq 80 nmol/L) [36].

Vitamin D Deficiency

Nutrient deficiencies are usually the result of dietary inadequacy, impaired absorption and use, increased requirement, or increased excretion. A vitamin D deficiency can occur when usual intake is lower than recommended levels over time, exposure to sunlight is limited, the kidneys cannot convert vitamin D to its active form, or absorption of vitamin D from the digestive tract is inadequate. Vitamin D-deficient diets are associated with milk allergy, lactose intolerance, and strict vegetarianism [37].

Rickets and osteomalacia are the classical vitamin D deficiency diseases. In children, vitamin D deficiency causes rickets, a disease characterized by a failure of bone tissue to properly mineralize, resulting in soft bones and skeletal deformities [29]. Rickets was first described in the mid-17th century by British researchers [29,38]. In the late 19th and early 20th centuries, German physicians noted that consuming 1-3 teaspoons of cod liver oil per day could reverse rickets [38]. In the 1920s and prior to identification of the structure of vitamin D and its metabolites, biochemist Harry Steenbock patented a process to impart antirachitic activity to foods [14]. The process involved the addition of what turned out to be precursor forms of vitamin D followed by exposure to UV radiation. The fortification of milk with vitamin D has made rickets a rare disease in the United States. However, rickets is still reported periodically, particularly among African American infants and children [29,38]. A 2003 report from Memphis, for example, described 21 cases of rickets among infants, 20 of whom were African American [38].

Prolonged exclusive breastfeeding without the AAP-recommended vitamin D supplementation is a significant cause of rickets, particularly in dark-skinned infants breastfed by mothers who are not vitamin D replete [6]. Additional causes of rickets include extensive use of sunscreens and placement of children in daycare programs, where they often have less outdoor activity and sun exposure [29,38]. Rickets is also more prevalent among immigrants from Asia, Africa, and the Middle East, possibly because of genetic differences in vitamin D metabolism and behavioral differences that lead to less sun exposure [29].

In adults, vitamin D deficiency can lead to osteomalacia, resulting in weak muscles and bones [7,8,15]. Symptoms of bone pain and muscle weakness can indicate inadequate vitamin D levels, but such symptoms can be subtle and go undetected in the initial stages.

Groups at Risk of Vitamin D Inadequacy

Obtaining sufficient vitamin D from natural food sources alone can be difficult. For many people, consuming vitamin D-fortified foods and being exposed to sunlight are essential for maintaining a healthy vitamin D status. In some groups, dietary supplements might be required to meet the daily need for vitamin D.

Breastfed infants

Vitamin D requirements cannot be met by human milk alone [5,39], which provides only about 25 IU/L [17]. A recent review of reports of nutritional rickets found that a majority of cases occurred among young, breastfed African Americans [40]. The sun is a potential source of vitamin D, but AAP advises keeping infants out of direct sunlight and having them wear protective clothing and sunscreen [41]. As noted earlier, AAP recommends that exclusively and partially breastfed infants be supplemented with 400 IU of vitamin D per day [18].

Older adults

Americans aged 50 and older are at increased risk of developing vitamin D insufficiency [28]. As people age, skin cannot synthesize vitamin D as efficiently and the kidney is less able to convert vitamin D to its active hormone form [5,42]. As many as half of older adults in the United States with hip fractures could have serum 25(OH)D levels <12 ng/mL (<30 nmol/L) [6].

People with limited sun exposure

Homebound individuals, people living in northern latitudes (such as New England and Alaska), women who wear long robes and head coverings for religious reasons, and people with occupations that prevent sun exposure are unlikely to obtain adequate vitamin D from sunlight [43,44].

People with dark skin

Greater amounts of the pigment melanin result in darker skin and reduce the skin's ability to produce vitamin D from exposure to sunlight. Some studies suggest that older adults, especially women, with darker skin are at high risk of developing vitamin D insufficiency [34,45]. However, one group with dark skin, African Americans, generally has lower levels of 25(OH)D yet develops fewer osteoporotic fractures than Caucasians (see section below on osteoporosis).

People with fat malabsorption

As a fat-soluble vitamin, vitamin D requires some dietary fat in the gut for absorption. Individuals who have a reduced ability to absorb dietary fat might require vitamin D supplements [46]. Fat malabsorption is associated with a variety of medical conditions including pancreatic enzyme deficiency, Crohn's disease, cystic fibrosis, celiac disease, surgical removal of part of the stomach or intestines, and some forms of liver disease [15].

People who are obese

Individuals with a body mass index (BMI) ≥ 30 typically have a low plasma concentration of 25(OH)D [47]; this level decreases as obesity and body fat increase [48]. Obesity does not affect skin's capacity to synthesize vitamin D, but greater amounts of subcutaneous fat sequester more of the vitamin and alter its release into the circulation. Even with orally administered vitamin D, BMI is inversely correlated with peak serum concentrations, probably because some vitamin D is sequestered in the larger pools of body fat [47].

Vitamin D and Health

Optimal serum concentrations of 25(OH)D for bone and general health throughout life have not been established [6,11] and are likely to vary at each stage of life, depending on the physiological measures selected. The three-fold range of cut points that have been proposed by various experts, from 16 to 48 ng/mL (40 to 120 nmol/L), reflect differences in the functional endpoints chosen (e.g., serum concentrations of parathyroid hormone or bone fractures), as well as differences in the analytical methods used. The numerous assays for 25(OH)D provide differing results. One reason for these issues of precision and variability is that no standard reference preparations or calibrating materials are available commercially to help reduce the variability of results between methods and laboratories. Efforts are underway to standardize the quantification of 25(OH)D to measure vitamin D status.

In March 2007, a group of vitamin D and nutrition researchers published a controversial and provocative editorial contending that the desirable concentration of 25(OH)D is ≥ 30 ng/mL (≥ 75 nmol/L) [12]. They noted that supplemental intakes of 400 IU/day of vitamin D increase 25(OH)D concentrations by only 2.8-4.8 ng/mL (7-12 nmol/L) and that daily intakes of approximately 1,700 IU are needed to raise these concentrations from 20 to 32 ng/mL (50 to 80 nmol/L).

Osteoporosis

More than 25 million adults in the United States have or are at risk of developing osteoporosis, a disease characterized by fragile bones that significantly increases the risk of bone fractures [50]. Osteoporosis is most often associated with inadequate calcium intakes (generally $<1,000$ - $1,200$ mg/day), but insufficient vitamin D contributes to osteoporosis by reducing calcium absorption [51]. Although rickets and osteomalacia are extreme examples of the effects of vitamin D deficiency, osteoporosis is an example of a long-term effect of calcium and vitamin D insufficiency [52]. Adequate storage levels of vitamin D maintain bone strength and might help prevent osteoporosis in older adults, nonambulatory individuals who have difficulty exercising, postmenopausal women, and individuals on chronic steroid therapy [53].

Normal bone is constantly being remodeled. During menopause, the balance between these processes changes, resulting in more bone being resorbed than rebuilt. Hormone therapy with estrogen and progesterone might be able to delay the onset of osteoporosis. However, some medical groups and professional societies recommend that postmenopausal women consider using other agents to slow or stop bone resorption because of the potential adverse health effects of hormone therapy [54-56].

Most supplementation trials of the effects of vitamin D on bone health also include calcium, so it is not possible to

isolate the effects of each nutrient. The authors of a recent evidence-based review of research concluded that supplements of both vitamin D₃ (at 700-800 IU/day) and calcium (500-1,200 mg/day) decreased the risk of falls, fractures, and bone loss in elderly individuals aged 62-85 years [6]. The decreased risk of fractures occurred primarily in elderly women aged 85 years, on average, and living in a nursing home. Women should consult their healthcare providers about their needs for vitamin D (and calcium) as part of an overall plan to prevent or treat osteoporosis.

African Americans have lower levels of 25(OH)D than Caucasians, yet they develop fewer osteoporotic fractures. This suggests that factors other than vitamin D provide protection [57]. African Americans have an advantage in bone density from early childhood, a function of their more efficient calcium economy, and have a lower risk of fracture even when they have the same bone density as Caucasians. They also have a higher prevalence of obesity, and the resulting higher estrogen levels in obese women might protect them from bone loss [57]. Further reducing the risk of osteoporosis in African Americans are their lower levels of bone-turnover markers, shorter hip-axis length, and superior renal calcium conservation. However, despite this advantage in bone density, osteoporosis is a significant health problem among African Americans as they age [57].

Cancer

Laboratory and animal evidence as well as epidemiologic data suggest that vitamin D status could affect cancer risk. Strong biological and mechanistic bases indicate that vitamin D plays a role in the prevention of colon, prostate, and breast cancers. Emerging epidemiologic data suggest that vitamin D has a protective effect against colon cancer, but the data are not as strong for a protective effect against prostate and breast cancer, and are variable for cancers at other sites [58-59]. Studies do not consistently show a protective effect or no effect, however. One study of Finnish smokers, for example, found that subjects in the highest quintile of baseline vitamin D status have a three-fold higher risk of developing pancreatic cancer [60].

Vitamin D emerged as a protective factor in a prospective, cross-sectional study of 3,121 adults aged ≥ 50 years (96% men) who underwent a colonoscopy. The study found that 10% had at least one advanced cancerous lesion. Those with the highest vitamin D intakes (>645 IU/day) had a significantly lower risk of these lesions [61]. However, the Women's Health Initiative, in which 36,282 postmenopausal women of various races and ethnicities were randomly assigned to receive 400 IU vitamin D plus 1,000 mg calcium daily or a placebo, found no significant differences between the groups in the incidence of colorectal cancers over 7 years [62]. More recently, a clinical trial focused on bone health in 1,179 postmenopausal women residing in rural Nebraska found that subjects supplemented daily with calcium (1,400-1,500 mg) and vitamin D₃ (1,100 IU) had a significantly lower incidence of cancer over 4 years compared to women taking a placebo [63]. The small number of cancers reported (50) precludes generalizing about a protective effect from either or both nutrients or for cancers at different sites. This caution is supported by an analysis of 16,618 participants in NHANES III, where total cancer mortality was found to be unrelated to baseline vitamin D status [64]. However, colorectal cancer mortality was inversely related to serum 25(OH)D concentrations; levels >80 nmol/L were associated with a 72% risk reduction than those <50 nmol/L.

Further research is needed to determine whether vitamin D inadequacy in particular increases cancer risk, whether greater exposure to the nutrient is protective, and whether some individuals could be at increased risk of cancer because of vitamin D exposure [58].

Other conditions

A growing body of research suggests that vitamin D might play some role in the prevention and treatment of type 1 [65] and type 2 diabetes [66], hypertension [67], glucose intolerance [68], multiple sclerosis [69], and other medical conditions [70-71]. However, most evidence for these roles comes from in vitro, animal, and epidemiological studies, not the randomized clinical trials considered to be more definitive. Until such trials are conducted, the implications of the available evidence for public health and patient care will be debated.

A recent meta-analysis found that use of vitamin D supplements was associated with a reduction in overall mortality from any cause by a statistically significant 7% [72-73]. The subjects in these trials were primarily healthy, middle aged or elderly, and at high risk of fractures; they took 300-2,000 IU/day of vitamin D supplements.

Health Risks from Excessive Vitamin D

Vitamin D toxicity can cause nonspecific symptoms such as nausea, vomiting, poor appetite, constipation, weakness,

and weight loss [74]. More seriously, it can also raise blood levels of calcium, causing mental status changes such as confusion and heart rhythm abnormalities [8]. The use of supplements of both calcium (1,000 mg/day) and vitamin D (400 IU/day) by postmenopausal women was associated with a 17% increase in the risk of kidney stones over 7 years in the Women's Health Initiative [75]. Deposition of calcium and phosphate in the kidneys and other soft tissues can also be caused by excessive vitamin D levels [5]. A serum 25(OH)D concentration consistently >200 ng/mL (>500 nmol/L) is considered to be potentially toxic [15]. In an animal model, concentrations ≤400 ng/mL (≤1,000 nmol/L) were not associated with harm [16].

Excessive sun exposure does not result in vitamin D toxicity because the sustained heat on the skin is thought to photodegrade previtamin D₃ and vitamin D₃ as it is formed [11,30]. High intakes of dietary vitamin D are very unlikely to result in toxicity unless large amounts of cod liver oil are consumed; toxicity is more likely to occur from high intakes of supplements.

Long-term intakes above the UL increase the risk of adverse health effects [5] (Table 4). Substantially larger doses administered for a short time or periodically (e.g., 50,000 IU/week for 8 weeks) do not cause toxicity. Rather, the excess is stored and used as needed to maintain normal serum 25(OH)D concentrations when vitamin D intakes or sun exposure are limited [15,76].

Table 4: Tolerable Upper Intake Levels (ULs) for Vitamin D [5]

Age	Children	Men	Women	Pregnancy	Lactation
Birth to 12 months	25 mcg (1,000 IU)				
1-13 years	50 mcg (2,000 IU)				
14+ years		50 mcg (2,000 IU)	50 mcg (2,000 IU)	50 mcg (2,000 IU)	50 mcg (2,000 IU)

Several nutrition scientists recently challenged these ULs, first published in 1997 [76]. They point to newer clinical trials conducted in healthy adults and conclude that the data support a UL as high as 10,000 IU/day. Although vitamin D supplements above recommended levels given in clinical trials have not shown harm, most trials were not adequately designed to assess harm [6]. Evidence is not sufficient to determine the potential risks of excess vitamin D in infants, children, and women of reproductive age.

Interactions with Medications

Vitamin D supplements have the potential to interact with several types of medications. A few examples are provided below. Individuals taking these medications on a regular basis should discuss vitamin D intakes with their healthcare providers.

Steroids

Corticosteroid medications such as prednisone, often prescribed to reduce inflammation, can reduce calcium absorption [77-79] and impair vitamin D metabolism. These effects can further contribute to the loss of bone and the development of osteoporosis associated with their long-term use [78-79].

Other medications

Both the weight-loss drug orlistat (brand names *Xenical*® and *allii*™) and the cholesterol-lowering drug cholestyramine (brand names *Questran*®, *LoCholest*®, and *Prevalite*®) can reduce the absorption of vitamin D and other fat-soluble vitamins [80-81]. Both phenobarbital and phenytoin (brand name *Dilantin*®), used to prevent and control epileptic seizures, increase the hepatic metabolism of vitamin D to inactive compounds and reduce calcium absorption [82].

Vitamin D and Healthful Diets

According to the 2005 *Dietary Guidelines for Americans*, "nutrient needs should be met primarily through consuming foods. Foods provide an array of nutrients and other compounds that may have beneficial effects on health. In certain cases, fortified foods and dietary supplements may be useful sources of one or more nutrients that otherwise might be

consumed in less than recommended amounts. However, dietary supplements, while recommended in some cases, cannot replace a healthful diet."

The *Dietary Guidelines for Americans* describes a healthy diet as one that

- Emphasizes a variety of fruits, vegetables, whole grains, and fat-free or low-fat milk and milk products.
Milk is fortified with vitamin D, as are many ready-to-eat cereals and a few brands of yogurt and orange juice. Cheese naturally contains small amounts of vitamin D.
- Includes lean meats, poultry, fish, beans, eggs, and nuts.
Fish such as salmon, tuna, and mackerel are very good sources of vitamin D. Small amounts of vitamin D are also found in beef liver and egg yolks.
- Is low in saturated fats, *trans* fats, cholesterol, salt (sodium), and added sugars.
Vitamin D is added to some margarines.
- Stays within your daily calorie needs.

For more information about building a healthful diet, refer to the *Dietary Guidelines for Americans* (<http://www.health.gov/dietaryguidelines/dga2005/document/default.htm>) and the U.S. Department of Agriculture's food guidance system, *My Pyramid* (<http://www.mypyramid.gov>).

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The mission of the Office of Dietary Supplements (ODS) is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population.

General Safety Advisory

Health professionals and consumers need credible information to make thoughtful decisions about eating a healthful diet and using vitamin and mineral supplements. These Fact Sheets provide responsible information about the role of vitamins and minerals in health and disease. Each Fact Sheet in this series received extensive review by recognized experts from the academic and research communities.

The information is not intended to be a substitute for professional medical advice. It is important to seek the advice of a physician about any medical condition or symptom. It is also important to seek the advice of a physician, registered dietitian, pharmacist, or other qualified health professional about the appropriateness of taking dietary supplements and their potential interactions with medications.

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