

# REVIEWING THE SCIENCE VITAMIN D<sub>2</sub> AND VITAMIN D<sub>3</sub>

## Meeting the shortfall of this important nutrient

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### Vitamin D: An Introduction

Vitamin D has been on Earth for 500 million years. Its first form came from phytoplankton. For reasons that are not precisely known, animals evolved to require it for the maintenance of their ossified skeletons. For more than a century, vitamin D has been recognized as the “anti-rachitic” factor, i.e., required to prevent the deficiency disease known as rickets.

Vitamin D is not a true vitamin, in the sense of it being a vital nutrient that we can *only* obtain by consuming it in the diet. It is rather a prohormone that, while available in foods, is primarily synthesized in our skin when we have had sufficient sun exposure. Pollution, northerly latitudes with less sun, sunscreen, or being shut indoors for extended periods can all adversely affect our vitamin D status.

Vitamin D deficiency and suboptimal intake is common across different age groups in the US adult population.<sup>1</sup> Because of the strong epidemiological link between vitamin D deficiency and major chronic diseases and all-cause mortality, it is critical that shortfalls of this essential nutrient are addressed.

## Vitamin D and Bone Health

Vitamin D plays a role in bone health by promoting the absorption and utilization of calcium. Deficiency or sub-optimal vitamin D status is common among older women.<sup>2,3</sup> At least two meta-analyses have found that supplementation with 700-800 IU per day of vitamin D protected bone in elderly individuals, whereas lower amounts (e.g., 400 IU/d) appear to be insufficient to produce this effect.<sup>4,5</sup> The protective effect of vitamin D against fractures is due in part to a reduction in bone loss.<sup>6,7</sup> In addition, most but not all, studies have found that vitamin D prevents fractures by enhancing muscle strength and balance, thereby reducing the incidence of falls in frail elderly people. In most of the studies in which vitamin D was effective, the reduction in the number of falls was around 50%. The minimum dosage of vitamin D that protected against falls was 800 IU per day.<sup>8</sup>

## Vitamin D and Immune Function

Vitamin D is a pro-hormone. As such, it is required for much more than just maintaining calcium and phosphorus balance in the body. Although the interaction between vitamin D and the immune system has been recognized for almost 30 years, research has accelerated in the last few years and the physiological relevance of vitamin D-mediated immunity has become clearer. Studies using human cells and animal models have highlighted potent effects of vitamin D on both innate and adaptive immune responses in a wide variety of tissues. From an epidemiological perspective, Vitamin D insufficiency has been linked with prevalent immune disorders. From a mechanistic perspective, Vitamin D is seen to be a key factor linking Innate and Adaptive immunity. Cells from the immune system convert vitamin D into its active forms, which in turn promotes antimicrobial responses to pathogens in macrophages; regulates maturation of antigen-presenting dendritic cells; balances T-lymphocyte (T cell) function; and stimulates development of suppressor regulatory T cells.<sup>9</sup> A general protective effect of vitamin D supplementation in the upper respiratory tract has been observed. The effect was greater in those with vitamin D deficiency and if the supplement was given daily or weekly, but not if given as large bolus doses.<sup>10</sup>

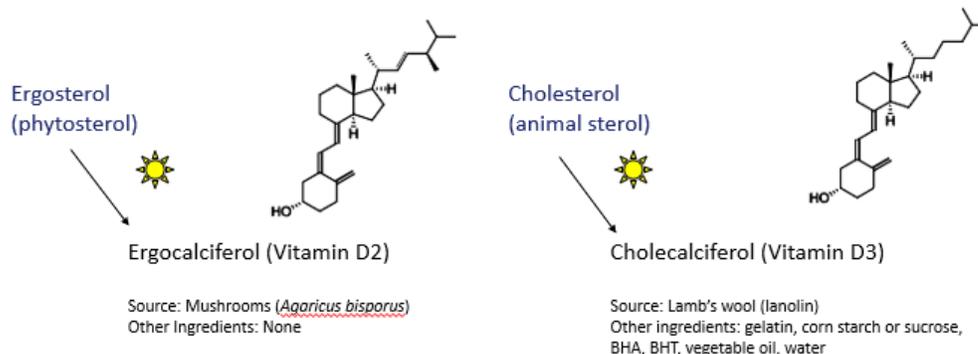
## Vitamin D and Longevity

Studies suggest that low vitamin D status could be associated with higher mortality from life-threatening conditions that collectively account for 60% to 70% of total mortality in high-income countries.<sup>11,12</sup> In a pooled analysis of 18 randomized trials, including a total of 57,311 participants, supplementation with vitamin D (mean dose of 528 IU per day; mean follow up period, 5.7 years) was associated with a significant 7% decrease in mortality.<sup>13</sup>



## FORMS OF VITAMIN D

The term Vitamin D refers collectively to the vitamers D2 (ergocalciferol) and D3 (cholecalciferol) and their metabolites, which are all functional in the body. People rarely get just one form of vitamin D. Dietary vitamin D2 comes primarily from plants, yeasts, and fungi; dietary vitamin D3 comes mostly from animals, although a supplemental form can also be produced from lichen. Both D2 and D3 require irradiation (e.g., from sun exposure) to be formed from their sterol precursors: ergosterol, a phytosterol, is transformed into ergocalciferol (D2); cholesterol, an animal sterol, is transformed into cholecalciferol (D3).



Until relatively recently, all food fortification of vitamin D was with D2.<sup>14</sup> Vitamin D3 is now occasionally used, but D2 is still more abundant, cost-effective, and has less ecological impact. In addition to making vitamin D in our skin, we can also obtain D3 from certain animal foods, such as beef liver, cheese, egg yolks, and fatty fish. Vitamin D3 sold as a supplement typically is derived from sheep's wool (lanolin). Ergocalciferol (D2) can also be synthesized pharmaceutically and is available as a high-dose prescription medicine.

### Is one form of vitamin D more effective?

Vitamin D metabolism is complex and remains a subject of debate and intensive research. Researchers do not all agree about the comparative efficiency of vitamin D2 and vitamin D3. While both D2 and D3 effectively replenish the body's vitamin D stores, a few studies have found D3 to be slightly more effective than D2 at raising 25(OH)D levels.<sup>15-19</sup> Some of these studies reached that conclusion based on bolus dosing of pharmacologic rather than physiologic doses, i.e., 50-300,000 IU weekly or monthly, which is not how most people take vitamin D. Most people use 600 - 2,000 IU (15-50 mcg) daily. At these amounts, most studies have shown no significant difference in total 25(OH)D levels.<sup>20-25</sup>

Research specifically investigating vitamin D2 from mushrooms has found that it effectively raises 25(OH)D comparably to D3.<sup>24,25</sup> It is also worth mentioning that newer research on the protective effect of vitamin D in the upper respiratory tract occurs with daily supplementation, but *not* weekly or monthly bolus dosing.<sup>10</sup>

***“The two major forms of vitamin D, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol), have been reported to exhibit identical responses in the body, so for the purpose of converting from IU to mcg, we consider them to be bioequivalent.”***

Center for Food Safety and Applied Nutrition (CFSAN), US Food and Drug Administration (FDA). *Converting Units of Measure for Folate, Niacin, and Vitamins A, D, and E on the Nutrition and Supplement Facts Labels: Guidance for Industry.* August, 2019

Under conditions of daily use, several studies have shown no difference between D2 and D3 in terms of their ability to replenish vitamin D, which is consistent with the official positions adopted by FDA and the European Food Safety Authority (EFSA):

Study	Conclusions
Biancuzzo RM, Clarke N, Reitz RE, Travison TG, Holick MF. Serum concentrations of 1,25-dihydroxyvitamin D2 and 1,25-dihydroxyvitamin D3 in response to vitamin D2 and vitamin D3 supplementation. <i>J Clin Endocrinol Metab.</i> 2013 Mar;98(3):973-9.	1000 IU/d of D2 or D3 produced <b>similar increases in serum 25(OH)D concentrations</b> and did not significantly alter serum concentrations of total 25(OH)D.
Fisk CM, Theobald HE, Sanders TA. Fortified malted milk drinks containing low-dose ergocalciferol and cholecalciferol do not differ in their capacity to raise serum 25-hydroxyvitamin D concentrations in healthy men and women not exposed to UV-B. <i>J Nutr.</i> 2012 Jul;142(7):1286-90.	Low-dose D2- and D3-fortified drinks were <b>equipotent in increasing 25(OH)D</b> in healthy men and women with negligible UV-B exposure, compared to placebo. There was <b>no difference between D2 and D3 groups</b> in the incremental AUC of their respective metabolites.
Gallo S, Phan A, Vanstone CA, Rodd C, Weiler HA. The change in plasma 25-hydroxyvitamin D did not differ between breast-fed infants that received a daily supplement of ergocalciferol or cholecalciferol for 3 months. <i>J Nutr.</i> 2013 Feb;143(2):148-53.	The increase in the 25(OH)D concentration among the D2 and D3-supplemented infants <b>did not differ</b> , suggesting daily intake of either isoform is acceptable for infants <4 mo.
Holick MF, Biancuzzo RM, Chen TC, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. <i>J Clin Endocrinol Metab.</i> 2008 Mar;93(3):677-81.	Supplementation with 1000 IU/d of <b>D2 was as effective as 1000 IU/d of D3</b> at maintaining serum 25(OH)D concentrations.
Keegan RJ, Lu Z, Bogusz JM, Williams JE, Holick MF. Photobiology of vitamin D in mushrooms and its bioavailability in humans. <i>Dermatoendocrinol.</i> 2013 Jan 1;5(1):165-76.	2000 IU/d of <b>D2 from mushrooms was as effective as 2000 IU/d of D2 or D3 from supplements</b> in raising and maintaining serum 25(OH)D concentrations.

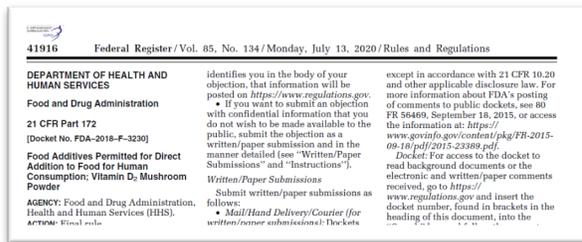
Both vitamin D2 and D3 can clearly achieve the clinical aims of vitamin D supplementation by replenishing the body's stores. Sunlight exposure is also essential, as it is the primary way our vitamin D needs are met. A recent Clinical Practice Guideline developed by The Endocrine Society recommends treatment with either Vitamin D2 or D3 for individuals with low serum 25(OH)D levels.<sup>26</sup> Notably, two scientists representing opposite sides of the D2 vs D3 debate (Holick and Heaney) are co-authors of this recommendation.

***“When controlled studies were conducted to assess D2 vs. D3 at nutritional rather than pharmacological levels, it has been repeatedly shown that the two vitamers are similar...”***

## Vitamin D2 in Supplementation and Food Fortification

Earthlight® Whole Food Vitamin D is a vegan, whole-food source of vitamin D from 100% button and portobello mushrooms (*Agaricus bisporus*), milled to powder. It is non-GMO, made in USA, and delivers 1,000 mcg (40,000 IU) of vitamin D (as ergocalciferol, or Vitamin D2) per gram.

Regulatory agencies, such as the United States FDA and the European Food Safety Authority have approved Earthlight mushroom vitamin D2 as effective and valid for food fortification and dietary supplementation, and regulate it as equipotent to vitamin D3 when taken daily at nutritional levels.



For the consumer who desires a vegan, non-GMO, minimally processed, whole food source of vitamin D to supplement their diet, Earthlight mushroom vitamin D2 represents an efficacious, ecologically sustainable, clean-label option.

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