VITAMIN D – ARE WE GETTING OUR FAIR SHARE?

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FOOD REGULATION IN THE UNITED STATES

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INTRODUCTION

More than 40 percent of American adults are deficient in vitamin D.[1] "Once foods were fortified with vitamin D and rickets appeared to have been conquered, many health care professionals thought the major health problem resulting from vitamin D deficiency had been resolved. However, rickets can be considered the tip of the vitamin D—deficiency iceberg."[2] Research during the past two decades has illustrated the importance of this essential vitamin in reducing the risk of many chronic illnesses, including cancer,[3-4] multiple sclerosis,[5] heart disease, autoimmune disease , infectious diseases, and type 1 diabetes mellitus.[6]

It is estimated that 50 000-63 000 individuals in the United States die prematurely from cancer annually due to insufficient vitamin D. The U.S. economic burden due to vitamin D insufficiency from inadequate exposure to solar ultraviolet B (UV-B), diet, and supplements was estimated at $40-56 billion

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[1] S. Allen, *Vitamin D Deficiency Tied to Host of Dangers,* The Boston Globe, December 30, 2004, also available at: http://www.boston.com/news/globe/health_science/articles/2004/12/30/vitamin_d_deficiency_tied_to_host_of_dangers/ (last accessed September 24, 2008).
[2] Michael F. Holick, *Vitamin D Deficiency,* 357 N. Engl. J. Med. 266(July 19, 2007).
[3] Garland C.F. & Garland F.C., *Do Sunlight and Vitamin D Reduce the Likelihood of Colon Cancer?* 9 Int. J. Epidemiol. 227-231 (1980).
[4] William B. Grant, *An Estimate of Premature Cancer Mortality in the U.S. Due to Inadequate Doses of Solar Ultraviolet-B Radiation.* 94 Cancer 1867-1875 (2002).
[5] Hayes C. E. et al, *Vitamin D and Multiple Sclerosis,* 216 Pro. Soc. Exp. Biol. Med. 21-27 (1997).
[6] Michael F. Holick, *Vitamin D: Importance in the Prevention of Cancers, type 1 diabetes, heart disease, and Osteoporosis,* 79 American Journal of Clinical Nutrition, 362-371 (2004).

in 2004. In contrast, the economic burden for excess UV irradiance was estimated at $6-7 billion.[7]

The current vitamin D intake recommendation from the Food and Nutrition Board, issued in 1997, calls for 200 IU (International Units) from birth through age 50; 400 IU from 51 through age 70 and 600 IU from 71 on.[8] Before 1997, the Recommended Daily Allowance for vitamin D in infants and children was 400 IU.[9] In essence, the scientific basis for this dose was that it approximated the same amount of vitamin D that was in a teaspoon of cod liver oil, which had long been considered safe and effective in preventing rickets.[10] Over forty years ago, an expert committee on vitamin D provided only anecdotal support for what it referred to as "the hypothesis of a small requirement" for vitamin D in adults, recommending one-half of the infant dose to ensure that adults were obtaining some from the diet.[11] The adult Dietary Reference Intake (DRI) of 200 IU/d was described as "a generous allowance" in the 1989 version of the American Recommended Dietary Allowance. The basis for these recommendations was made before it was possible to measure the circulating concentration of 25-Hydroxyvitamin D [25(OH)D], the indicator of the

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[7] William B. Grant, et all, *Comparisons of Estimated Economic Burdens due to Insufficient Solar Ultraviolet Irradiation and Vitamin D and Excess Solar UV Irradiance for the United States,* 81 Photochem. and Photobiol. , 1276-1286 (April 30, 2007)
[8] Food and Nutrition Board, Institute of Medicine, *Dietary Reference Intake for Calcium, Magnesium, Phosphorus, Vitamin D, and fluoride.* Washington, DC: National Academy Press (1997).
[9] National Academy of Science, *Recommended Dietary Allowances,* 10th ed. National Academy Press, Washington, DC (1989)
[10] E.A. Park, *The Therapy of Rickets,* 115 J. Am. Med. Assoc., 370-379 (1940).
[11] R. Blumberg, et al, *The Prophylactic requirement and the toxicity of vitamin D,* 31 Pediatrics, 512-525 (1963).

nutritional vitamin D status.[12]

Using a daily intake of 400IU vitamin D/d, which is the value used for nutrient labeling in the United States,[13] as well as the recommendation for older adults (age 51-70 y)[14], during an extended period of time, has little or no affect[15]. At this dose in an adult, the circulating 25(OH)D concentration usually remains unchanged or declines.[16]

Given the results of recent scientific studies that have evaluated high-dose vitamin D supplementation, it appears that the current DRI is woefully inadequate, misleading, and potentially harmful, placing individuals at undue risk for a number of chronic diseases. The current dietary recommendation of 200-600 IU/d is extraordinarily low compared with endogenous (produced inside organisms) production during sun exposure. Reexamination of the requirements for vitamin D is clearly merited and may likely reveal the need for vitamin D intakes to exceed the current dietary recommendations.

I. BACKGROUND

A. Historical Perspective

The history of vitamin D deficiency and its health consequences were first appreciated with the industrialization of northern Europe. The severe pollution caused by the burning of coal, along with the building of housing and industrial

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[12] Bruce W. Hollis, *Assessment of Vitamin D Nutritional and Hormonal Status: What to Measure and How to do it,* 58 Calcif. Tissue Int., 4-5 (1996).
[13] See 21 CFR §101.9
[14] Food and Nutrition Board, Institute of Medicine, *Dietary Reference Intake for Calcium, Magnesium, Phosphorus, Vitamin D, and fluoride.* Washington, DC: National Academy Press (1997).
[15] S. Datta, et all, *Vitamin Deficiency in Pregnant Women from a non-European Ethnic Minority Population—an International Study,* 109 Br. J. Obstet. Gyneaecol., 905-908 (2002).
[16] Reinhold Vieth, et al, *Wintertime Vitamin D Insufficiency is Common in Young Canadian Women, and their Vitamin D Intake does not Prevent it,* 55 Eur. J. Clin. Nutr. 1091-1097 (2001).

structures in such close proximity to one another, essentially eliminated sun exposure for children, which resulted in the bone-deforming disease commonly known as rickets. This disease was caused by sun deprivation and became the scourge of the industrialization of northern Europe and the northeastern United States. By the turn of the 20th century, it was estimated that 80-90% of children living in Leiden, Netherlands, and in Boston, USA, suffered from rickets.[17]

The lack of sunlight and its association with the devastating bone-deforming disease rickets in children was first recognized by Sniadecki in 1822.[18] The Viennese physician, Huldschinski, reported in 1919 that children with rickets who were exposed to a mercury arc lamp had radiologic improvement in their condition. This was quickly followed by the observation of Hess and Unger in 1921, that rachitic children who were exposed to sun light showed dramatic healing of their rachitic lesions.[19] In the early 1930s, the US government set up an agency to provide recommendations to parents about the beneficial effect of sensible exposure to sunlight for the prevention of rickets.[20] It was Steenbock[21] who realized that if one could irradiate children and animals to prevent rickets, then one should be able to irradiate food. This resulted in the UV irradiation of cows, their diet, and ultimately their milk to impart antirachitic activity. This further lead to the fortification of milk in the 1930s with 100 IU vitamin D_2 per 8

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[17] Michael F. Holick, *Resurrection of Vitamin Deficiency and Rickets,* 116 J. Clin. Invest. 2062-2072 (2006).
[18] *Jerdzej Sniadecki (1768-1838) on the Cure of Rickets.* (1840) Cited by W. Mozolowski, 143 Nature, 121-124 (1939)
[19] A.F. Hess & L.J. Unger , *The Cure of Infantile Rickets by Sunlight,* 77 JAMA, 39 (1921)
[20] Michael F. Holick, *Resurrection of Vitamin Deficiency and Rickets,* 116 J. Clin. Invest. 2062-2072
[21] H. Steenbock, *The Induction of Growth-Prompting and Calcifying Properties in a Ratio Exposed to Light.* 60 Science, 224-225 (1924).

ounces, which was responsible for the eradication of rickets in the United States and Europe.[22] The unfortunate outbreak of hypercalcemia during the 1950s in Great Britain was blamed on the overfortification of milk with vitamin D, even though there was little evidence to support this[23]. Because milk was scarce at the end of the war, many local stores that sold milk would add vitamin D to it if it was not purchased by the expiration date. This was thought to extend the shelf-life of the vitamin D-fortified milk. This rise in the incidence of hypercalcemia in infants in the 1950s resulted in Europe forbidding the fortification of dairy products with vitamin D.

B. Overview

Vitamin D obtained its name in the early part of the 20th century after the discovery of the antirachitic effects of cod liver oil. The suspected vitamin in cod liver oil was designated "D," as vitamins A, B, and C had already been identified.[24] The term "vitamin D" specifically refers to two biologically inert precursors: vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol).[25] Vitamin D_3 is produced in the skin from 7-dehydrocholesterol (DHC) in cell membranes after exposure to UV radiation in the UV-B spectrum (290-320 nm).[26]

Vitamin D_2 is plant derived, produced exogenously (derived externally) by

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[22] Michael F. Holick, *Resurrection of Vitamin Deficiency and Rickets,* 116 J. Clin. Invest. 2062-2072 (2006).
[23] A British Pediatric Association Report, *Infantile Hypercalcemia, Nutritional Rickets, and Infantile Scurvy in Great Britain,* 1 Br. Med. J., 1659-1661 (1964)
[24] T.R. Welch, et al, *Vitamin D—Deficient Rickets: The Reemergence of a once-conquered disease,* 137 J. Pediatr. 143-145 (2000).
[25] Michael F. Holick, *The Use and Interpretation of Assays for Vitamin D and its Metabolites,* 120(Suppl) J. Nutr., 1464-1469 (1990).
[26] Michael F. Holick, *the Cutaneous Photosynthesis of Previtamin D3: A Unique Photoendocrine System,* 77 J. Invest. Dermatol. 51-58 (1981).

irradiation of ergosterol, and enters the circulation through diet.[27] Vitamin D_3, like vitamin D_2, is available from foods and vitamin supplements. It can enter the circulation through gastrointestinal (GI) absorption.

Once vitamin D enters the circulation, it is metabolized in the liver to its primary circulating form, 25-hydroxyvitamin D [25(OH)D][28] and then in the kidneys, into its active form $1,25(OH)_2D$.[29-30] Many other tissues in the body, including macrophages (large cells protecting against infection), brain, colon, prostate, breast, and others, have the enzymatic machinery to locally produce $1,25(OH)_2D$.[31-32] Once produced by the kidneys, it enters the circulation and travels to its major target tissue the intestine and bone, where it interacts with its vitamin D receptor to enhance intestinal calcium and phosphorus absorption.[33]

The local production of $1,25(OH)_2D$ in non-calcium-regulating tissues such as the colon, prostate, and breast is thought to be for purpose of regulating up to 200 genes, which helps to control cell growth and cellular differentiation and may be responsible for decreasing the risk of the cell being transformed into

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[27] Prema B. Rapuri et al, *Effects of Vitamins D2 and D3 supplement use on serum 250HD concentration in elderly women in summer and winter.* 74 Calcif. Tissue Int. 150-156 (2004).
[28] The circulating concentration of 25(OH)D is a good reflection of cumulative effects of exposure to sunlight and dietary intake of vitamin D. It is used to determine a patient's vitamin D status.
[29] Hormonal form.
[30] Hector Deluca, *Overview of General physiologic features and Functions of Vitamin D,* 80 Am. J. Clin. Nutr., 1689-1696 (2004).
[31] H.S. Cross, et al, *25-Hydroxyvitamin D3-1-hydroxylase and Vitamin D Receptor Gene Expression in Human Colonic Mucosa Elevated During Early Cancerogenesis,* 66 Steroids 287-292 (2001).
[32] V. Tangpricha, et al, *25-Hydroxyvitamin D-1α-hydroxylase in Normal and Malignat Colon Tissue,* 357 Lancet, 1673-1674 (2001).
[33] Michael F. Holick, M. Garabedian, Vitamin D: Photobiology, Metabolism, Mechanism of Action, and Clinical Application. In: Favus MJ, ed. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 6th ed. Washington, DC: American Society for Bone and Mineral Research, 129-137 (2006).

malignant state, inhibiting cancer cell growth.[34]

Vitamin D intake from food and nutrient supplements is expressed in either international units (IU) or micrograms (μg). The biological activity of 1 μg of vitamin D equals 40 IU, and 1 IU equals 0.005 μg 25(OH)D.[35]

C. US Current Intake Recommendation

The guidelines currently in place within the United States recommend:

- 200 IU (5 μg) /day of vitamin D for children and younger adults
- 400 IU (10 μg)/day for those ages 51-70
- 600 IU (15 μg)/day for those over age 70.[36]

These guidelines are based on maintaining bone health.

II. Importance of Vitamin D Sufficiency at Various Stages of Life

A. Pre and Postnatal

One of the primary roles of vitamin D is the regulation of calcium and phosphorus absorption and metabolism for bone health. This role is especially important during pregnancy and lactation because bones develop rapidly during this period. Human milk contains little vitamin D (approximately 20 IU per liter), and women who are vitamin D-deficient provide even less to their breast–fed infants.[37]

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[34] Sunil Nagpal, et al, *Noncalcemic Action of Vitamin D Receptor Ligands,* 26 Endocr. Rev. 662-687 (2005).
[35] Food and Nutrition Board, Institute of Medicine, *Dietary Reference Intake for Calcium, Magnesium, Phosphorus, Vitamin D, and fluoride.* Washington, DC: National Academy Press 255 (1997).
[36] Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intake for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Washington, DC: The National Academies Press, 263-277 (1997).
[37] Bruce W. Hollis & C.L. Wagner, *Vitamin D Requirements During Lactation: High-dose*

Low birth weight (LBW) appears to be a consequence of vitamin D insufficiency during pregnancy. Insufficient serum 25(OH)D level disrupts calcium homeostasis, leading to intrauterine growth retardation, premature labor, and hypertension, all of which are risk factors for LBW infants.[38] This supports the hypothesis that African American and Asian-Indian mothers have much higher rates of LBW infants in the United States than do European Americans or Hispanic Americans.[39-40] This may be in part because Hispanic Americans have a slightly higher consumption of vitamin D than African Americans,[41] as well as lighter skin. Also, Koreans born in winter tend to have lower bone mineral density (BMD) than those born in summer.[42]

Children born prematurely are likely to have enamel defects in both primary and permanent teeth.[43] Maternal vitamin D sufficiency is required for proper fetal tooth development,[44-45] as well as adequate calcium. An additional benefit of sufficient vitamin D and calcium during pregnancy is good maternal bone health. Studies report 2-4 percent bone density losses during pregnancy are

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*maternal Supplementation as Therapy to prevent Hypovitaminosis D for both the Mother and the Nursing Infant.*6 Am. J. Clin. Nutr. 1752S-1758S (2004)

[38] Kathleen E. Fuller, *Low Birth-weight infants: the continuing ethnic disparity and the interaction of biology and environment,* 10 Ethn. Dis. 432-445 (2000).

[39] Greg R. Alexander, et al. *US Birth Weight/Gestation Age-Specific Neonatal Mortality: 1995-1997 Rates for Whites, Hispanics, and Blacks,* 111 Pediatrics (e61-e66)

[40] Jeffrey B. Gould, et all, *Perinatal Outcome in Two Dissimilar Immigrant Populations in the United States: a Dual Epidemiologic Paradox.* Pediatrics e676-e682 (2003)

[41] Mona S. Calvo, et al, *Vitamin D fortification in the United States and Canada: Current Status and Data Needs,* 80 Am. J. Clin. Nutr. A710S-1716S (2004).

[42] Ran Namgung & Reginald C. Tsang, *Bone in the Pregnant Mother and Newborn at Birth,* 333 Clin Chim Acta, 1-11 (2003).

[43] L. Aine, et al, *Enamel Defects in Primary and Permanents teeth of children Born Prematurely,* 29 J. Oral Pathol. Med. 403-409 (2000)

[44] Bonny Specker, *Vitamin D Requirements During Pregnancy,* 80 Am. J. Clin. Nutr., 1740S-1747S (2004).

[45] R.J. Purvis, et al, *Enamel Hypoplasia of the Teeth Associated with Neonatal Tetany: A Manifestation of Maternal Vitamin-D deficiency,* 2 Lancet, 811-814 (1973)

exacerbated by calcium and vitamin D deficiency.[46]

Maternal and infant 25(OH)D sufficiency appears to greatly reduce the risk of type 1 diabetes mellitus (DM).[47] It is also linked to significant reduction of risk for multiple sclerosis (MS).[48]

A study in England found birth seasonality was related to later diagnosis of bipolar disorder,[49] strongly suggesting that the risk of bipolar disorder can be reduced through sufficient vitamin D intake during pregnancy.

Insufficient vitamin D intake during infancy can result in reduced bone mineralization, slower growth, bone deformities, and increased risk of fracture — the hallmarks of rickets.[50] Indeed, rickets has been reported among breast-fed African-American infants in several southern states.[51-52]

B. Youth and Adolescence

The primary role of sufficient vitamin D during youth and adolescence is optimization of BMD. For example, serum 25(OH)D levels were found to be strongly correlated with BMD for peripubertal Finnish girls[53] and young Finish

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[46] Bonny Specker, *Vitamin D Requirements During Pregnancy,* 80 Am. J. Clin. Nutr., 1740S-1747S (2004).
[47] Elina Hypponen, et al, *Intake of Vitamin D and Risk of Type 1 Diabetes: a Birth-cohort Study,* 358 Lancet, 1500-1503 (2001).
[48] Ashton F. Embry, *Vitamin D Supplementation in the Fight Against Multiple Sclerosis,* 19 J. Orthomolecular Med., 27-38 (2004).
[49] E.H. Hare & J.S. Price, *Mental Disorder and Season of birth: Comparison of Psychoses with Neurosis.* 115 Br. J. Psychiatry, 533-540 (1969)
[50] Nicola Pawley & Nick J. Bishop, *Prenatal and Infant Predictors of Bone Health: the Influence of Vitamin D.* 80 Am. J. Clin. Nutr., 1748S-1751S (2004).
[51] S.R. Kreiter, et al, *Nutritional Rickets in African American Breast-fed Infants*, 137 J. Pediatr., 153-157 (200).
[52] Pamela Weisberg, et al, *Nutritional Rickets Among Children in the United States: Review of Cases Reported between 1986 and 2003,* 80 Am. J. Clin. Nutr., 1697S– 1705S (2004).
[53] Marjo KM Lehtonen-Veromaa, et al, *Vitamin D and Attainment of Peak Bone Mass Among Peripubertal Finnish Girls: a 3-year Prospective study,* 76 Am. J. Clin. Nutr., 1446-1453 (2002).

men.[54]

Another important role of vitamin D during youth appears to be in reducing the risk of MS.[55] It is known that the risk of MS increases rapidly with the increasing of latitude.[56] The best explanation for this latitudinal variation is strengthening of the immune system, especially in winter, which can then help prevent viral infections from giving rise to MS.[57,58,59]

C. Adulthood

Vitamin D levels in adulthood are important for maintaining BMD. The factors for low BMD, osteoporosis, and osteopenia include vitamin D insufficiency, inadequate calcium intake, lack of exercise, and other dietary factors. Serum 25(OH)D levels have been directly related to bone health in men and women of all ages.[60]

Another benefit of vitamin D is maintenance of optimal muscle strength. Vitamin D deficiency can cause osteomalacia, which is associated with muscle and bone pain.[61-62]

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[54] Ville V. Valimaki, et al, *Vitamin D Status as a Determinant of Peak Bone Mass in Young Finnish Men.* 89 J. Clin. Endocrinol. Met., 76-80 (2004).
[55] I. A. Van der Mei, et al, *Past Exposure to Sun, Skin Phenotype, and Risk of Multiple Sclerosis: Case-control Study, 327 BMJ 316 (2003).*
[56] M.T. Wallin, et al, *Multiple sclerosis in US Veterans of the Vietnam Era and Later Military Service: Race, Sex, and Geography.* 55 Ann. Neurol. 65-71 (2004).
[57] C.E. Hayes, et al., *the Immunological Functions of the Vitamin D Endocrine System,* 49 Cell. Mol. Biol., 277-300 (2003).
[58] Margheritia T. Cantona, *Vitamin D and Autoimmunity: Is Vitamin D Status an Environmental Factor Affecting Autoimmune Disease Prevalence?* 223 Proc. Soc. Exp. Biol. Med., 223-230 (2000).
[59] Ashton F. Embry, *Vitamin D Supplementation in the Fight against Multiple Sclerosis,* 19 J. Orthomolecular Med., 27-38 (2004).
[60] Heike A. Bischoff-Ferrari, et al, *Effect of Vitamin D on Muscle Strength and Relevance in Regard to Osteoporosis Prevention.* 62 Z. Rheumatol, 518-521 (2003).
[61] Michel F. Holick, *Vitamin D deficiency: What a Pain it is,* 78 Mayo Clin. Proc., 1457-1459 (2003).
[62] Erik F. Eriksen & Henning Glerup, *Vitamin D deficiency and aging: Implications for General*

Sufficient vitamin D levels in adulthood may significantly reduce the risk for many types of cancer. The interest in vitamin D as risk reduction factor for cancer began in 1980 when Cedric and Frank Garland looked at maps of cancer mortality in the United States and noticed colon cancer rates were lowest in the southwest.[63] In trying to determine a mechanism, they reasoned that the primary physiological effect of exposure to sun, other than including tanning, was the production of vitamin D. A few years later they demonstrated than colon cancer risk was inversely associated with pre-diagnostic serum 25(OH)D levels.[64] It was soon demonstrated that breast, ovarian, and prostate cancer also had inverse correlations with solar UV-B radiation.[65] Additional cancers found to be vitamin D sensitive are cervical, gall bladder, laryngeal, oral, pancreatic, and Hodgkin's lymphoma. [66] It is now thought that UV-B and vitamin D reduce the risk of 17 types of cancer.[67,68,69]

Presently, the role of UV-B and vitamin D in reducing the risk of cancer is considered a scientific finding that satisfies most, if not all the criteria for

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Health and Osteoporosis. 3 Biogerontology, 73-77 (2002).

[63] Cedric F. Garland & F.C. Garland, *Do Sunlight and Vitamin D Reduce the Likelihood of Colon Cancer?* 9 Int. J. Epidemiol., 227-231 (1980).

[64] Cedric Garland, et al, *Dietary Vitamin D and Calcium and Risk of Colorectal Cancer: a 19-year prospective study in men.* 1 Lancet, 307-309 (1985).

[65] D. Michael Freedman, et al, *Sunlight and Mortality from Breast, Ovarian, colon, prostate, and non-melanoma skin cancer: a Composite Death Certificate Based Case-Control Study.* 59 Occup. Environ. Med., 257-262 (2002).

[66] William B. Grant, *Benefits of UVB Exposure to Reduce the Risk of Cancer—Ecologic Studies of Cancer Mortality Rates. Proceedings of the CIE Symposium '04; Light and Health: non-visual Effects, 30 Sep.-2 Oct.2004, Commission International de L'Eclairage,* Vienna, Austria, 174-177 (2004).

[67] Id.

[68] William B. Grant, *An estimate of Premature Cancer Mortality in the U.S. due to inadequate doses of Solar Ultraviolet-B Radiation,* 94 Cancer, 1867-1875 (2002).

[69] William B. Grant & C.F. Garland, *A Critical Review of Studies on Vitamin D in Relation to Colorectal Cancer,* 48 Nutr. Cancer. 115-123 (2004).

causality in a biological system given by Hill.[70-71] The most important criteria appear to be: (1)strength of association; (2) consistency in results for different populations; (3) generally linear dose-response gradients; (4) exclusion of possible confounding factors from explaining the observations; and (5) identification of mechanisms to explain the observations.

Tuberculosis (TB) is often associated with lower serum 25(OH)D levels among patients and increased risk among those with low serum 25(OH)D levels.[72]

D. Elderly Population

The elderly have a particularly strong need to maintain vitamin D sufficiency. Not only are they likely to produce less vitamin D from solar UV-B irradiation because they generally expend less time in sunlight than do younger people,[73-74] but their efficiency of photoproduction is less.[75] In addition, diseases such as cancer and osteoporotic fractures are most likely among the elderly.

Cancer is a disease for which incidence and mortality rates generally increase with age and there is generally a time lag between dietary effects and discovery of cancer. A 23-year lag between the introduction of Western dietary factors, reduced total dietary fiber, and colon cancer was found for Japan after

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[70] Austin B. Hill, *the Environment and Disease: Association or Causation?* 58 Proc. R. Soc. Med., 295-300 (1965)
[71] Nancy Potischman & Douglas L. Weed, *Causal Criteria in Nutritional Epidemiology, Am. J. Cli. Nutr., 1309S-1314S (1999).*
[72] T.Y. Chan, *Vitamin D Deficiency and Susceptibility to Tuberculosis,* 66 Calcif. Tissue Int., 476-478 (2000).
[73] Michael F. Holick, *The Photobiology of Vitamin D and its Consequences for Humans,* 453 Ann. N.Y. Acd. Sci., 1-13 (1985).
[74] Michael F. Holick, *Environmental Factors that influence the Cutaneous Production of Vitamin D,* 61 Am. J. Clin. Nutr., 638S-645S (1995).
[75] Michael F. Holick, *Photosynthesis of Vitamin D in the Skin: Fed. Proc., 1876-1882 (1987).*

1947.[76] Exercise is associated with reduced risk for cancer,[77] and the elderly generally exercise less than their younger counterparts.

Osteoporotic fractures are of significant concern for the elderly. Severe factors contribute to the risk of such fractures, including low BMD, muscle weakness, and neurological control of balance/neuromuscular function. [78] Vitamin D sufficiency, adequate dietary calcium and related minerals, as well as exercise help reduce the risk of falls and fractures.[79-80]

An added benefit is reduced tooth loss.[81]

III. SOURCES OF VITAMIN D

A. Sunlight

Sunlight exposure is by far the most important source of vitamin D. The human skin has a large capacity for vitamin D production.[82] Anything that diminishes the transmission of solar UV-B radiation to the earth's surface or anything that interferes with the penetration of UVB radiation into the skin will affect the cutaneous synthesis of vitamin D.[83] Melanin (skin pigment) is extremely efficient in absorbing UV-B radiation, and, thus, increased skin

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[76] Keisuke Tsuji, et al, *Time-lag Effect of Dietary Fiber and Fat Intake Ratio on Japanese Colon Cancer,* 9 Biom. Environ. Sci., 223-228 (1996).
[77] Kim C. Westerlind, *Physical Activity and Cancer Prevention—Mechanisms,* 35 Med. Sci. Sports. Exerc., 1834-1840 (2003).
[78] Jugdeep K. Dhesi, *Vitamin D Supplementation Improves Neuromuscular Function in Older People Who Fall,* 33 Age Ageing, 589-595 (2004).
[79] Michael F. Holick &A.O. Malabanan, *Vitamin D and Bone Health in Postmenopausal Women*, 12 J. Women's Health, 151-156 (2003).
[80] Kai M. Chan, et al, *Exercise Interventions: Defusing the World's Osteoporosis Time Bomb,* 81 Bull World Health Organ, 827-830 (2003).
[81] Elizabeth A. Krall, et al, *Calcium and Vitamin D Supplements Reduce Tooth Loss in the Elderly,* 111 Am. J. Med., 452-456 (2001).
[82] A.R. Webb, et al, *An Evaluation of the relative contributions of exposure to Sunlight and of Diet to the circulating Concentrations of 25-hydroxivitamin D in an elderly Nursing Home Population in Boston, 51 Am. J. Clin. Nutr., 1075-1081(1990).*
[83] Michael F. Holick, *Vitamin D: A Millennium Perspective,* 88 J. Cell. Biochem., 296-307 (2003).

pigmentation markedly reduces vitamin D_3 synthesis. For instance, a Caucasian individual in a bathing suit who is not tanned will release ≈10,000-20,000 IU vitamin D_3 into the circulation within 24 h of exposure, after a whole-body exposure from ≈10-12 min of peak July summer sun (11:30 to 14:30 h EST) in Boston.[84] For an Asian Indian it would take perhaps 30 min of exposure, and, for a very darkly pigmented African-American, it could require 120 min of exposure to synthesize the same amount of vitamin D_3 as a Caucasian exposed for 10-12 min.[85] Similarly, a sunscreen with a sun protection of 15 absorbs 99% of the incident UV-B radiation, and when topically applied properly will decrease the synthesis of vitamin D_3 in the skin by 99%.[86] African Americans with very dark skin have an SPF (sun protection factor) of 15, thus, their ability to make vitamin D in their skin is reduced as much as 99%.[87-88] This along with decreased milk intake are the explanations for why most African Americans who live in a temperate climate are vitamin D deficient, whereas Africans living near the equator where vitamin D_3 synthesis is more efficient because of the higher flux of UV-B photons are not.[89-90]

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[84] Excessive exposure to sunlight does not cause vitamin D3 intoxication because any excess previtamin D3 or vitamin D3 is destroyed by sunlight.
[85] T.L. Clements, et al, *Increased Skin Pigment Reduces the capacity of skin to synthesize Vitamin D3,* Lancet, 74-76 (1982).
[86] L.Y. Matsuoka, et al, *Sunscreens suppress Cutaneous vitamin D3 synthesis,* 64 J. Clin. Endocrinol Metab., 1165-1168 (1987).
[87] Tai C. Chen, et al, *Factor that Influence the Cutaneous Synthesis and Dietary Sources of Vitamin D,* 460 Arch. Biochem. Biophys., 213-217 (2007)
[88] T.L. Clements, et al, *Increased Skin Pigment Reduces the capacity of skin to synthesize Vitamin D3,* Lancet, 74-76 (1982).
[89] A.R. Webb, et al, *Influence of Season and latitude on the Cutaneous Synthesis of vitamin D3: Exposure to Winter Sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin,* 67 J. Clin Endocrinol Metab. 373-378 (1988).
[90] T.D. Thacher, et al, *Nutritional Rickets around the world: Causes and Future Directions,* 26 Ann Trop. Paediatr. 1-16 (2006).

The angle at which the sun reaches the earth has a dramatic effect on the number of UV-B photons that reach the earth's surface.[91] This is why when the zenith angle is increased during the wintertime and in the early morning and late afternoon, little if any vitamin D_3 synthesis occurs.[92-93]

The clothing style is also important, black clothes exclude 100% UV-B.[94] Those who practice purdah, whereby all skin is covered and the skin is prevented from being exposed to sunlight, are risking vitamin D deficiency and explains why in the sunniest areas of the world vitamin D deficiency can be very common in both children and adults.[95]

Aging is associated with decreased concentrations of 7-dehydrocholesterol, the precursor of vitamin D_3 in the skin. A 70-y-old has ≈25% of 7-dehydrocholesterol that a young adult does and thus has 75% reduced capacity to make vitamin D_3 in the skin.[96]

Glass and plastic interfere with the penetration of UV-B radiation into the skin, excluding 100% of this type of radiation.[97]

In addition, indoor tanning using artificial lamps with a UV spectral output that mimics that of solar UV radiation reaching the earth's surface near

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[91] A.R. Webb, et al, *Influence of Season and latitude on the Cutaneous Synthesis of vitamin D3: Exposure to Winter Sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin,* 67 J. Clin Endocrinol Metab. 373-378 (1988).
[92] Id.
[93] Michael F. Holick, *Vitamin D: A Millennium Perspective,* 88 J. Cell. Biochem., 296-307 (2003).
[94] L.Y. Matsuoka, et al, *Clothing prevents ultraviolet-B radiation-dependent Photosynthesis of Vitamin D3,* 75 J. Clin. Endocrinol. Metab., 1099-1103 (1992).
[95] Saleh H. Sedrani, *Low 25-hydroxyvitamin D and normal serum calcium concentrations in Saudi Arabia: Riyadh Region, 28 Ann. Nutr. Metab. 181-185 (1984.)*
[96] Michael F. Holick, et al, *Age, Vitamin D, and Solar Ultraviolet,* 2(8671) Lancet, 1104-1105 (1989).
[97] Michael F. Holick, *McCollum Award Lecture, 1994: Vitamin D-New Horizons for the 21st Century,* 60 Am. J. Nutr., 619-630 (1994).

summertime noon at midlatitude (3-5% UV-B, 95-97% UV-A) can also be used to produce vitamin D.[98] Lower fractions of UV-B, such as 1.5 % in France and Sweden, are associated with increased risk of melanoma.[99] However, those who do not tan easily should not use such lamps since they are less well protected against free radical formation.[100]

B. Food

1. Animal Source

Few foods naturally contain vitamin D: those that do include oily fish such as salmon, mackerel, sardines, and herring and oils from fish, including cod liver oil. Wild-caught salmon typically contains 500-1000 IU vitamin D_3/100 g (3.5 ounces). However, salmon farmed in the United States receive very little vitamin D in their pelleted diet and contain just ≈100-250 IU vitamin D_3/100 g serving.[101] Farmed salmon from Norway are fed fish, and thus contain a similar amount of vitamin D_3 in their flesh as wild-caught salmon. Liver and other organ meats are also high in vitamin D but are not as popular as fish and are often avoided because of their high cholesterol content. Egg yolk contains 25 IU vitamin D_3/100 g serving.[102]

2. Plant Source

Most of the few foods that naturally contain vitamin D are from animal

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[98] Vin Tanpricha, et al, *Tanning is Associated with Optimal Vitamin D Status(Serum 25-OHD Concentration) and higher Bone Mineral Density,* 80 Am. J. Clin. Nutr., 1645-1649 (2004).
[99] Philippe Autier, *Perspectives in Melanoma Prevention: The Case Sunbeds,* 40 Eur. J. Cancer, 2367-2376 (2004).
[100] Irina Terenetskaya, *Two Methods for Direct Assessment of the Vitamin D Synthetic Capacity of Sunlight and Artificial UV Sources.* 89-90 J. Steroid Biochem. Mol. Biol., 623-626.
[101] Tai C. Chen, et al, *Factors that Influence the Cutaneous Synthesis and Dietary Sources of Vitamin D,* 460 Arch. Biochem. Biophys., 213-217 (2007).
[102] Id.

origin. For that reason, strict vegetarians, who are not consuming even milk, are at risk of vitamin D deficiency disorders. The Food and Drug Administration (FDA) has been seeking non-animal food that is rich in vitamin D. This search led the FDA to mushrooms, according with Mona S. Calvo, Ph.D., who is an expert regulatory scientist at the FDA, Center for Safety and Applied Nutrition, "Mushrooms are the only natural fresh vegetable or fruit that contains vitamin D".[103] In nature, wild mushrooms contain very small amounts of vitamin D_2.[104] Even though mushrooms are deficient in vitamin D_2, earlier researchers have found them to be rich source of ergosterol (vitamin D_2 precursor).[105-106] After exposure to UV-B light, for a short period of time, mushrooms provide a significant amount of vitamin D in the form of vitamin D_2.[107] The level of vitamin D increases to many times the minimal daily requirements, [400 IU (10 μg)][108]. Normally, a serving (84 g/3 oz) of white button mushrooms contains 15 IU (0.38 μg). A standard serving size of white button mushrooms exposed post-harvest to UV-B for 5 minutes contains 86.9 μg (3 476 IU) vitamin D_2 or 869% of the Daily

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[103] *The Mushroom Marketplace*, Quarterly Retail Grocery Newsletter from the Mushroom Council, Vol. I, Issue I, 1st Quarter (2008). Also available at: http://www.mushroomcouncil.com/export/sites/default/retail/RetailNewsletter2008_5.9.08-USDA_APPROVED.pdf (last accessed November 22, 2008)

[104] Pirjo H. Mattila, *Sterol and Vitamin D2 Contents in Some Wild and Cultivated Mushrooms,* 76 Food Chem., 293-298 (2002).

[105] Id.

[106] The highest ergosterol content was found in button mushrooms (7.8 ± 0.35 mg/g DM) while the lowest was in enoki mushrooms (0.68 ± 0.14 mg/g DM). See V.J. Jasinghe & C.O. Perera (2005).

[107] Viraj J. Jasinghe & C.O. Perera, *Distribution of Ergosterol in Different Tissues of Mushrooms and its Effect on the Conversion of Ergosterol to Vitamin D2 by UV Irradiation,* 92 Food Chem., 541-546 (2005).

[108] Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intake for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Washington, DC: The National Academies Press, 263-277 (1997).

Value.[109] At the same time, 5 g (0.18 oz) of fresh shiitake mushrooms irradiated for 15 min with UV-A, or UV-B is more than enough to obtain the recommended allowances of vitamin D for adults (10 μg/day)[110]

The Agricultural Research Service of the USDA is studying the time and dosage of the UV-B light treatment up to 4 days post-harvest and D_2 degradation during storage.[111] Some other studies have demonstrated that by using a Pulsed UV-B lamp[112] the content of vitamin D_2 in mushrooms can be increased up to 800% DV/serving in a very short exposure time of about 1 sec.[113]

Mushrooms show great promise as a natural, non-animal source of vitamin D. That being the case, there are some obstacles the mushroom industry has to overcome, these involve not only production-line technology, shelf-life, and bioavailability (measure of drug absorption) of the vitamin, but also to obtain regulatory approval from FDA for the use of UV radiation to increase vitamin D_2 content of mushrooms. There is currently no regulation regarding Vitamin D_2; nevertheless, the Vitamin D_3 regulation (21CFR § 172.380) can be referenced as a guideline.

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[109] Mona S. Calvo, *FDA's Center for Food Center and Applied Nutrition and the Mushroom Council Collaborate to Optimize the Natural Vitamin D Content of Edible Mushrooms and to Examine their Health Benefits in Different Rodent Models of Innate Immunity,* Presented at 12th Annual FDA Science Forum: Pioneering the Future of Public Health. April 18-20, 2006. Washington Convention Center. Also available at: http://www.cfsan.fda.gov/~frf/forum06/O-01.htm (last accessed September 14, 2008).

[110] Viraj J. Jasinghe & C.O. Perera, *Ultraviolet Irradiation: The Generator of Vitamin D2 in edible mushrooms,*95 Food Chem., 638-643 (2006).

[111] John S. Roberts, et al, *Vitamin D2 Formation from Post-Harvest UV-B Treatment of Mushrooms (Agaricus bisporus) and Retention During Storage,* 56 J. Agric. Food Chem., 4541-4544 (2008).

[112] Pulse UV lamps deliver a broad spectrum light (100-800 nm) along with high intensity pulses in a short amount of time (e.g. 3 pulses per second).

[113] Robert Beelman & M.D. Kalaras, *Vitamin D2 Enrichment in Fresh Mushrooms Using Pulsed UV Light,* Department of Food Science, Penn State University (2008). For more information contact: Robert B. Beelman Ph.D.

There are two regulatory pathways the industry can take: (1) convince FDA the use of UV irradiation is already covered under the use of UV and pulsed light for surface microbial control (21CFR§179.39 and §179.41), and (2) in order to make the Vitamin D_2 nutrition content claim and to use the UV process, two petitions would have to be approved by FDA. This is because, under the Federal Food, Drug and Cosmetic Act (21 USC 301 et seq.), irradiation falls under the food additive definition and nutrient supplements fall under the food additive regulations.

Mushrooms have the potential to become a nutraceutical[114] or functional[115] food. "They may even be the Omega-3 egg of the produce section". From darkness to the "sunshine miracle".

3. Food Fortification

The addition of vitamin D to foods is very carefully regulated in the United States. Its addition to foods as a nutrient supplement is in accordance with 21CFR 184.1 (b) (2), its use has strict limitations with respect to the categories of foods, functional use, and level of use.[116] In accordance with 21CFR 184.1 (b) (2), any addition of vitamin D to foods not in compliance with each of these established limitations requires a food additive regulation. Such regulatory limitations provide a control mechanism that limits overfortification with vitamin D and thus eliminates some of the concerns regarding the increasing fortification

[114] A food or naturally occurring food supplement thought to have a beneficial effect on human health.
[115] Any foodstuff enhanced by additives and marketed as beneficial to health and longevity.
[116] US Food and Drug Administration, *Direct food substances affirmed as generally recognized as safe,* Also available at: http://www.access.gpo.gov/nara/cfr/waisidx_04/21cfr184_04.html (last accessed November 22, 2008)

of foods with calcium that is currently underway in the United States.[117]

Unlike Canada, where fortification with vitamin D is mandatory for designated foods, the addition of vitamin D to eligible foods in the United States is optional in most cases, with the exception of fortified milk[118] (400 IU/quart or 946 mL). Fluid milk in the United States is not required to have vitamin D added unless the label declares that is fortified[119] (400 IU/quart or 946 mL). Vitamin D, which includes crystalline vitamin D_2 and D_3 and vitamin D_2 and D_3 resin formed from the irradiation of ergocalciferol and cholecalciferol, can be added as the sole source of added vitamin D in the food categories shown below and must not exceed the specified limitations. [120]

Category of food	Maximum levels in food (as served)	Functional use
Breakfast cereals, §170.3(n)(4) of this chapter	350 (IU/100 grams)	Nutrient supplement, §170.3(o)(20) of this chapter.
Grain products and pastas, §170.3(n)(23) of this chapter	90(IU/100 grams)	Do.
Milk, §170.3(n)(30) of this chapter	42 (IU/100 grams) 400 IU/quart or 946mL	Do.
Milk products, §170.3(n)(31) of this chapter	89 (IU/100 grams)	Do.

Vitamin D is also affirmed as generally recognized as safe (GRAS) for the use in infant formula [21CFR184.1950(c)(2)] and as an optional ingredient in margarine (131 IU/100g) [21CFR184.1950 (c)(3)]. Vitamin D_3 is regulated as a direct food additive for use as a nutrient supplement in calcium-fortified fruit juices and fruit

[117] N.A. Sutton, *The Safety of Calcium Fortification,* 83 Med. Health, 364-366 (2000).
[118] *21CFR131.127 Nonfat dry milk fortified with vitamin A and D and 21 CFR131.130 Evaporated milk, fortified*
[119] *21CFR131.110*
[120] *21CFR184.1950(c)(1)*

juice drinks (100 IU/RACC) (921CFR172.380). In addition, vitamin D may be added to olestra to compensate for any interference with absorption of fat-soluble vitamins, in accordance with 21CFR172.867 (14)(d).

Although many varieties of foods are eligible for controlled levels of vitamin D fortification, there is a large gap between the number of eligible foods and the number and variety of vitamin D-fortified foods observed in the US marketplace. For example, milk products such as yogurt, butter, ice cream, sour cream, cream, cottage cheese, and most varieties of hard and soft cheeses are not routinely fortified with vitamin D, which calls attention to a significant public misperception that all dairy products are rich sources of vitamin D.[121] Actually, fluid milk is the only dairy food that is routinely fortified with vitamin D. In the United States, milk and ready-to-eat cereals are the predominant food sources of vitamin D.[122]

Many of the barriers that keep the current vitamin D fortification practices from preventing Hypovitaminosis D are attributed to problems with the consumption of fluid milk. First, the amount of vitamin D added to milk may not be adequate to produce the desired health changes or even to increase circulating 25(OH)D concentrations. Second, milk is not uniformly consumed in the United States, and it has experienced pronounced declines in the overall consumption of milk in the past decade.[123] Furthermore, the racial/ethnicity groups at greatest

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[121] Mona S. Calvo, *Dietary Considerations to Prevent Loss of Bone and Renal Function,* 16 Nutrition, 564-566 (2000)
[122] Mona S. Calvo & S.J. Whiting, *Prevalence of Vitamin D Insufficiency in Canada and the United States: Importance to Health Status and Efficacy of Current Food Fortification and Dietary Supplement Use,* 61 Nutr. Rev., 107-113 (2003).
[123] Mona S. Calvo, *Dietary considerations to prevent loss of bone and renal function,* 16

risk of vitamin D insufficiency consume less milk and ready-to-eat cereal than do their white counterparts.[124]

C. Supplements

Individuals with unique dietary patterns, such as low milk consumption, vegetarian diet or low fish intakes and those who avoid sun exposure for various reasons, including fear of increased risk of skin cancer can prevent vitamin D deficiency/insufficiency by dietary supplementation. Multivitamins that contain 400 IU vitamin D and supplements containing vitamin D only are now available in various amounts including 400, 1 000, 2 000, 4 000, 5 000 and 50 000 IU vitamin D_3. The pharmaceutical form of vitamin D in the United States is vitamin D_2 and is available as 50 000 IU vitamin D_2 in a capsule or 8 000 IU vitamin D_2/mL. [125]

IV. NUTRITIONAL ADEQUACY FOR VITAMIN D

A. Optimal Vitamin D Levels

Although the overall vitamin D status can be easily estimated at a specified time point from measurements of plasma levels of total 25(OH)D, [126-127] which reflect both the amount of vitamin D produced in the skin and the amount absorbed from the intestine. The optimal range of 25(OH)D is still a subject of debate.

Nutrition, 564-566 (2000).
[124] Mona S. Calvo, S.J. Whiting, *Prevalence of Vitamin D Insufficiency of Current Food Fortification and Dietary Supplement Use,* 61 Nutr. Rev. 107-113 (2003).
[125] Michael F. Holick, *Resurrection of Vitamin D Deficiency and Rickets,* 116 J. Clin. Invst., 2062-2072 (2006).
[126] JS. Adams, et al, *Vitamin D synthesis and metabolism after ultraviolet irradiation of normal and vitamin D deficient subjects,* 306, N. Engl. J. Med., 722-725 (1982).
[127] H. Reichel, *The role of the Vitamin D endocrine system in health and disease,* 320, N. Engl. J. Med., 980-991 (1989).

It has been proposed that levels of 25(OH)D less than 20 to 25 nmol/L(nanomole per liter) as vitamin D **Deficiency**, levels from 25 to 50 nmol/L be classified as reflecting vitamin D **Insufficiency** , and values greater than 50 nmol/L as **sufficiency.**[128] Subsequent epidemiologic studies have disclosed that lower extremity function (8-food walking, sit-to-stand time), bone mineral density, fracture risk, periodontal disease, and risk of colon cancer depend on plasma levels of 25(OH)D with a threshold value for optimal plasma levels.[129] Based on these outcomes, the **optimal** plasma concentrations for 25(OH)D are typically between 75 and 100 nmol/L.[130] Some of these effects, notably the effects of vitamin D supplementation on muscle function, falls, and fractures have been confirmed in intervention studies and meta-analyses of randomized controlled studies.[131-132]

B. Target Vitamin D Intake Recommendations

Having defined optimal plasma levels of 25(OH)D for skeletal and non-skeletal health, it is necessary to estimate the amount of oral vitamin D that is necessary to obtain these levels. It has been claimed that doses high as high as 4 000 IU/day (100 μg) are needed,[133-134] although this view has been criticized.[135]

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[128] Reinhold Vieth, *Vitamin D supplementation 25-hydroxyvitamin D concentrations, and safety,* 69, 842-856 (1999)
[129] Heike A. Bischoff-Ferrari, et al, *Estimation of serum concentrations of 25- hydroxyvitamin D for multiple health outcomes,* 54, Am. J. Clin. Nutr., 18-28 (2006).
[130] Heike A. Bischoff-Ferrari, et al, *Estimation of serum concentrations of 25- hydroxyvitamin D for multiple health outcomes,* 54, Am. J. Clin. Nutr., 18-28 (2006).
[131] Heike A. Bischoff-Ferrari, et al, *Effect of vitamin D on falls: a meta-analysis,* 291, JAMA., *1999-2006 (2004)*
[132] Heike A. Bischoff-Ferrari, et al, *Fracture prevention with Vitamin D supplementation. A meta-analysis of randomized controlled trials,* 293, JAMA., 1257-1264 (2005).
[133]Reinhold Vieth, *Vitamin D Supplementation 25-hydroxyvitamin D Concentrations, and Safety,* 69 Am. J. Clin. Nutr., 842-856 (1996).
[134] Robert P. Heaney, et al, *Human serum 25-hydrocholecalciferol response to extended oral*

In a study performed in Finland, elderly women receiving a daily supplementation of 800 IU/day (20 μg) increased their plasma 25(OH)D levels to about 70 nmol/L when their dietary intake was 320-360 IU/day (8-9 μg).[136] Based on such dose relations, it has been estimated that a daily intake of 800-1 000 IU/day (20-25 μg) will be sufficient to maintain a plasma concentration of around 70-100 nmol/L in adult Caucasians.[137]

Other vitamin D experts indicate that if insufficiency is to be corrected, daily dietary intake of 850 IU (21.25 μg/day) to 2 000 IU (approximately 51 μg/day) is required.[138]

CONCLUSION

Vitamin D is beneficial at all stages of life. Therefore, there is an urgent need to recommend an intake of vitamin D in quantities that are effective. The current guidelines are based on maintaining bone health. Since 1997, much has been learned about the non-skeletal benefits of vitamin D, essentially making these guidelines incomplete and obsolete.

The cost of increasing the recommended intake of vitamin D would be substantially lower than the cost of buying the drugs used to cure the chronic diseases which are the results of vitamin D deficiency.

Due to the convincing facts that point toward the benefits of increased

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dosing with cholecalciferol, 77, Am. J. Clin. Nutr., 204-210 (2003).

[135] Frits A. Muskiet, et al, *Do we really need > or = 100 μg vitamin D/d, and is it safe for all of us?, 74,* Am. J. Clin. Nutr., 862-864 (2001).

[136] Christel Lamberg- Allardt, *Vitamin D in food and its supplements,* 92, Prog. Biophys. Mol. Biol., 33-38 (2006).

[137] Heike A. Bischoff-Ferrari, et al, *Estimation of serum concentrations of 25- hydroxyvitamin D for multiple health outcomes,* 54, Am. J. Clin. Nutr., 18-28 (2006).

[138] Connie M. Weaver & JC. Fleet, *Vitamin D requirements: current and future,* 80, Am. J. Clin. Nutr., 1735s-1739s (2004)

dietary consumption of vitamin D and the strong evidence of such consumption being safe, it is necessary that those who have the ability to support public health –the media, vitamin manufactures, and policy makers – start new initiatives that will have a realistic chance of making a difference in terms of vitamin D nutrition.