A REVIEW OF THE ADVERSE EFFECTS OF
EXCESSIVE INTAKES OF VITAMIN D

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by

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For each of these categories, a different standard of risk could be established, the Bureau Director explained, noting, for example, for traditional foods the acceptable level of risk would be considerably higher than that associated with traditional food additives.

Built into the system is a societal judgment, he said, asserting, in that way, "the debate over benefits could be resolved."

Miller suggested that the Delaney clause needs some modification which would allow debate over the question of carcinogenicity.

Modification of Delaney to allow for argument in the classification of a substance as a carcinogen, an argument based on scientific fact, he said, "might be a useful way of maintaining the important and necessary characteristics of Delaney and, at the same time, recognize scientific dispute."

He opposed use of risk-benefit assessments, saying that the category approach implies use of a benefit judgment.

The development of quantifiable and rational risk assessments and the permitting of argument on questions of safety of substances, such as carcinogens, Miller predicted, "will go a long way toward allowing the agency to develop rational regulations in the future without invoking risk-benefit to magically solve our problems."

During questioning, Miller also joked that the administrative process might work better without the "constant intrusions" of the lawyers who struggle with every word, comma, and period.

VITAMIN D SUPPLEMENTATION LIMIT TO 400 IU PER DOSE ON RX URGED BY FASEB

Limitation of vitamin D dose forms to 400 IU/dose and avoidance of any supplementation not prescribed by a physician were suggested by the Life Sciences Research Office of the Federation of American Societies for Experimental Biology recently.

The review of the adverse effects of vitamin D intake, prepared under contract to the Food and Drug Administration, apparently grew out of the review of vitamin D use in food by the Select Committee on GRAS (generally recognized as safe) Substances, which had called for further evaluation of vitamin D safety (See FOOD CHEMICAL NEWS, March 20, 1978, Page 18).

The Committee had offered to hold a hearing on the report (See FOOD CHEMICAL NEWS, June 19, 1978, Page 57), and Vitamins, Inc., had indicated interest in testifying, but later withdraw its request (See FOOD CHEMICAL NEWS, Oct. 2, 1978, Page 10).

The review found that, except in unusual cases, it seems unlikely that the toxic level of 1000 IU/kg over an extended period "would be exceeded from self medication with over-the-counter preparations."
However, it noted small children, especially infants, "would seem more vulnerable to supplementary vitamin D," since 8 to 12 supplemental doses of the 400 IU/capsule or dose pediatric supplements to a 5-kg infant would approach the toxic level.

Concluding that "the maximal safe and the minimal toxic doses for vitamin D appear to be in the range of 200-1000 IU/kg/day," the review noted:

"Data on the potential long-term deleterious effects of intakes within this broad range are virtually nonexistent and are urgently needed for proper nutritional and clinical management. Some individuals, particularly infants and small children, may already be approaching the lower limit of this range. There is a paucity of clinical observation or metabolic data on the effects of prolonged use of vitamin D supplements or preferential consumption of vitamin D-rich foods."

It suggested that a more precise definition of normal as well as potentially hazardous ranges of vitamin D intake may be reached through the rapidly evolving elucidation of vitamin D metabolism, together with the development of sensitive analytical tools.

FDA SELECTS TEN PESTICIDES FOR SURVEILLANCE INDEX

In the first step in setting up a complete Surveillance Index (SI) for Pesticides, the Food and Drug Administration has selected ten pesticides and ranked them for priority.

Establishment of the SI was one of the recommendations of an FDA study group which was headed by the agency's Scientific Coordinator, John R. Wessel (See FOOD CHEMICAL NEWS, Aug. 28, 1978, Page 14). In a Feb. 25 letter to Dr. David G. Lindsay, of England's Ministry of Agriculture, Fisheries and Food, Wessel disclosed that FDA's Bureau of Foods has "completed assessment of the first ten pesticides . . ."

FDA Associate Commissioner for Regulatory Affairs Joseph P. Hile on Feb. 15 wrote to Environmental Protection Agency Deputy Associate Administrator for Pesticide Programs Edwin Johnson that the first ten pesticides "are among those for which your agency has issued a rebuttable presumption against registration (RPAR)."

Hile said "special monitoring efforts" would be initiated on benomyl, maleic hydrazide, and pronamide. "FDA monitoring for one of the other ten pesticides -- DBCP -- has been already initiated in response to an EPA request," Hile wrote. He said that BHC, lindane, PCN, chlorobenzilate, and EPM are "included in FDA's ongoing monitoring programs . . ." The letter noted that chlorobenzilate is "only partially recovered by analytical methods used routinely in FDA programs." The tenth pesticide selected for monitoring is methyl thiophanate.

Wessel said the SI list will not be completed "until FDA has classified and supported the classification for each of the 300 plus pesticides that might occur in food from purposeful use, environmental sources, or use in foreign countries."
FOREWORD

The Federation of American Societies for Experimental Biology (FASEB) recognizes that its resources are particularly suited to marshalling scientific expertise for review and assessment of topics in the biological and medical sciences. The Life Sciences Research Office (LSRO) was established by FASEB in 1962 as an operational arm of the Executive Director's staff to provide a means for the conduct of such scientific review and analysis studies. Reports of LSRO studies are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators in specific areas of biology and medicine.

This technical report was prepared as Quick Response 14 for the Bureau of Foods, Food and Drug Administration in accordance with the provisions of FDA Contract No. 223-75-2090, Task II-A: "Quick Response Actions on Request". This report has been reviewed by the consultants listed in Section VII and their viewpoints and opinions were incorporated; however, the listing of their names does not necessarily imply endorsement of the conclusions of this report.

In accordance with the policies and guidelines developed by the LSRO Advisory Committee, this report has been reviewed and approved for submission by the Chairman of the LSRO Advisory Committee. Reports prepared by LSRO do not necessarily reflect the opinions of the individual members of FASEB constituent societies. The author and LSRO are solely responsible for the contents of this report.

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I. INTRODUCTION

The Select Committee on GRAS Substances (SCOGS, 1978) recently evaluated the health aspects of vitamins D₂ and D₃ as food ingredients. It concluded that the present level of the use of vitamin D is adequate to meet the needs for this essential nutrient, and there are no reasonable grounds to suspect that the level and manner of use in foods pose a hazard to the public. However, the margin of safety between prophylactic doses of the vitamin and the amounts reported to have produced toxic manifestations in some individuals is relatively low. The Select Committee cautioned that there appeared to be a need to limit intakes of vitamin D from all sources, including food and vitamin preparations. Because vitamin D supplements can be purchased without prescription, a potential danger of overdosage may exist among individuals who inadvertently or intentionally increase their intake in this manner.

The Food and Drug Administration (FDA) is attempting to establish a sound policy for controlling the potency of dietary supplements of vitamin D, based upon a critical review of available information of its toxicity. The FDA requested that the Life Sciences Research Office, Federation of American Societies for Experimental Biology, provide background information for this evaluation and identify, to the extent possible, the maximum safe limit of potency for vitamin D supplements.

II. BACKGROUND

Various expert committees have agreed that 400 International Units (IU) (10 μg) of vitamin D per day are adequate to meet the needs of individuals of all ages, including infants and lactating and pregnant women (Food and Nutrition Board, National Research Council, 1974; American Academy of Pediatrics, Committee on Nutrition, 1967; Food and Drug Administration, 1979). An Expert Committee of FAO/WHO (Anonymous, 1974), concluded that daily intake of 100 IU was adequate for adults (1-2 IU/kg) and for children aged 7 years or older (2-5 IU/kg). The Food and Nutrition Board (1974) cautioned that ingestion of vitamin D in excess of these recommended amounts provides no benefit, and that large excesses are potentially harmful.

The toxicity of excessive doses of vitamin D was first reported by Hess and Lewis (1928). They observed drowsiness, vomiting, loss of weight, and marked hypercalcemia in two infants receiving 5 mg irradiated ergosterol (vitamin D₂) (about 20,000-40,000 IU/kg) daily for 3 weeks. Since then, several hundred
cases of hypervitaminosis D have been reported among patients receiving large doses of the vitamin for a variety of conditions, especially those being treated for arthritis (Anning et al., 1948; Chaplin et al., 1951; SCOOGS, 1978). Diagnosis of hypervitaminosis D is difficult because many of the signs and symptoms are not unique to vitamin D toxicity, but are common to other disorders as well. Early symptoms include weakness, fatigue, malaise, dry mouth, vague muscle and bone pains, nausea, and thirst. Weight loss, diarrhea, anorexia, and vomiting may also occur. The most characteristic sign is an elevated serum calcium; the possibility of vitamin D toxicity is generally considered when calcium levels exceed 12 mg/dl serum (Hayes and Hegsted, 1973). The various effects of vitamin D toxicity have been attributed either to the direct effect of the hypercalcemia and accompanying electrolyte disturbances or to an indirect effect of calcification of critical organs (Food and Drug Administration, 1979). Anning et al. (1948) reported an average daily intake of 2080 IU vitamin D/kg body weight among 35 patients manifesting overt vitamin D toxicity. However, in many of the published cases it has been difficult for the reader of the reports to determine the vitamin D intakes which caused toxicity because the diagnostic criteria; dosage and duration of treatment; age, weight, and sex of patients; and the underlying pathology have not always been indicated.

Certain clinical disorders are characterized by a hypersensitivity to vitamin D. Infantile idiopathic hypercalcemia is generally included among this group, although it has not been demonstrated unequivocally that vitamin D is the responsible agent. Of 50 cases reported in a British survey in 1960-1961, 14 of the infants were stated to have received no vitamin D supplements before the onset of the disease (British Paediatric Association, 1964). Some, but not all, mildly affected infants demonstrated an exacerbation of hypercalcemia when challenged with vitamin D (Fraser et al., 1966). There is no evidence that women, whose offspring were severely affected in utero, had ingested more than 400-800 IU (7-13 IU/kg body weight) daily of vitamin D during pregnancy (Fraser et al., 1966). Indirect evidence implicating vitamin D in infantile idiopathic hypercalcemia was the sharp decline in reported cases in Great Britain when the fortification of milk, which had been approximately 1600 IU/l during the early 1950's, was reduced to 400 IU/l in 1957 (American Academy of Pediatrics, 1967). The reduced number of reported cases did not occur immediately but followed after an interval of 2-3 years. Most cases reported with either level of milk fortification were mild. It is not known whether the incidence of severe as well as mild cases also decreased when the vitamin D level in milk was reduced. Thus, while the decreased incidence in the disorder following the reduced fortification of milk is suggestive, the causal role of vitamin D intake in the pathogenesis of infantile idiopathic hypercalcemia must be considered unresolved.
Hypercalcemia has been frequently noted in sarcoidosis although the reported incidence varies widely (2-60%) (Avioli and Haddad, 1973). Some patients are especially sensitive to vitamin D and relatively small doses may induce an abnormally rapid rise in either serum or urinary calcium. Thus, the administration of 3000 IU (about 50 IU/kg) vitamin D₃ daily for 8 days to a patient with pulmonary sarcoidosis caused a rise in serum calcium from 10.0-12.4 mg/dl; the urinary calcium increased from 460-720 mg/24 hours (Papapoulos et al., 1979). The hypercalcemia in this disorder responds dramatically to cortisone therapy (Avioli and Haddad, 1973).

Some investigators (Linden, 1974; Kummerow, 1979) have suggested that long-term ingestion of excess vitamin D may be a factor in coronary heart disease, but this relationship has not been demonstrated convincingly.

In contrast with disorders which may predispose towards an increased sensitivity to vitamin D, other conditions are characterized by a relative insensitivity or resistance to the vitamin. Patients with vitamin-D resistant rickets, hypoparathyroidism, certain gastrointestinal or renal diseases, and those on anticonvulsant medication require supplementary and often massive doses of vitamin D for proper management (Avioli and Haddad, 1973; Marx et al., 1978).

The Select Committee (SCOGS, 1978), after a careful review of the literature, concluded that intakes of vitamin D in excess of 1000 IU/kg/day had been associated in some instances with evidence of toxicity, and that relatively long periods of administration were usually required for adverse effects to become recognizable. They also concluded that strikingly little information exists on the effects of 200-1000 IU/kg/day of vitamin D for all age groups. They emphasized that additional data within this range are needed before a safe maximal level of intake could be defined with confidence.

III. METABOLISM

Within the past decade, great strides have been made in elucidating the mechanism of vitamin D action, in large part through the investigations of DeLuca and his colleagues. Lund and DeLuca (1966) first demonstrated the existence of a metabolite with a biological potency greater than that of the native vitamin. This was later identified (Blunt et al., 1968) as 25-hydroxyvitamin D₃ (calcidiol) (25-OHD₃).* Later it was discovered that this

*The usual analytical techniques do not differentiate between vitamin D₂ and D₃ metabolites. When no subscript is employed, both D₂ and D₃ are implied.
compound, in turn, was converted in the kidney to a still more potent derivative, 1,25-dihydroxyvitamin D₃ (1,25-(OH)₂D₃) (calcitriol) (Holick et al., 1971). Calcitriol is generally accepted as the hormonal principle performing the known functions of vitamin D₃. It is ten times more active than vitamin D₃ itself in stimulating intestinal calcium transport, mobilizing calcium from the bone, and preventing and curing rickets. The production of 1,25-(OH)₂D₃ is markedly stimulated by hypocalcemia and depressed by hypercalcemia. This sensitivity to the calcium needs of the body is mediated through the parathyroids; it is abolished by parathyroidectomy but restored by injection of parathyroid hormone, which in turn stimulates the production of 1,25-(OH)₂D₃ (DeLuca, 1978, 1979). Additional metabolites of vitamin D have also been detected in the body, but their physiological significance has not been clearly established.

The development of analytical techniques to measure the various vitamin D metabolites in the blood may provide more sensitive, specific, and accurate measures of the vitamin D status of an individual than has been possible heretofore. Much of these efforts, have focused on 25-OHD, which appears to be the major circulating metabolite (Avioli and Haddad, 1973). In normal individuals, the 25-OHD serum level averages about 25 ng/ml (Arnaud et al., 1977; Gray et al., 1977; Haddad et al., 1977; Stamp and Round, 1974). Some variation, evident during different seasons of the year and in different geographic locations, apparently reflects the degree of exposure to sunlight. In the United States, values among preschool children averaged 23.5 ng/ml serum in winter and 35.2 ng/ml in summer (Arnaud et al., 1977). British investigators generally have reported lower values, ranging from 12.4-12.9 ng/ml in winter to 17-24 ng/ml in summer (Stamp and Round, 1974). The serum levels of eight lifeguards in the British Isles during midsummer averaged 64.4 ng/ml (Haddad and Chyu, 1971).

Haddad and Stamp (1974) found extremely low levels of 25-OHD (less than 3 ng/ml) in a "few" cases of vitamin D deficiency rickets. However, no significant correlation between vitamin D intake and 25-OHD₃ levels could be demonstrated among normal individuals on relatively low or moderate intakes (about 45-490 IU/day). With large doses of vitamin D, the levels of 25-OHD varied directly with the vitamin intake. Stamp et al. (1977) administered 1600-100,000 IU (about 25-1500 IU/kg) vitamin D₂ or D₃ daily, for periods of 4 months or longer, to 128 normal adult subjects or patients receiving vitamin D therapy. Serum calcium levels were not determined. No signs of toxicity were reported in any of the subjects. A linear relationship was found between the dose administered and the plasma levels of 25-OHD (Figure 1):
Figure 1. Plasma-25-OHD in 164 subjects receiving daily long-term treatment with vitamin D$_2$ or D$_3$ (●) and with 25-OHD$_3$ (○) in different doses. Regression lines (with 95% confidence limits) are given for each form of treatment. (From Stamp et al., 1977, with permission of the authors and publishers).

*1 mg vitamin D = 40,000 IU.
\[
\log y = 0.178 + 0.701 \log x
\]

where \( x = \) daily vitamin D dosage in \( \mu \)g, and \( y = \) plasma 25-OHD\(_3\) in ng/ml plasma

Thus, the corresponding 25-OHD plasma levels for daily intakes of 2000, 10,000, 20,000, 40,000, and 100,000 IU vitamin D per day for 4 months or longer, were about 20, 70, 120, 190, and 360 ng/ml plasma, respectively. Treatment with 25-OHD produced higher plasma levels than did vitamin D. An unstated number of adult subjects also received 1800-40,000 IU (about 30-600 IU/kg) vitamin D\(_2\) or D\(_3\) daily for 4 weeks. The plasma 25-OHD levels for these subjects were somewhat lower than those receiving the same dose for 4 months or longer. With 40,000 IU daily, the 25-OHD level after 4 weeks was 120 ng/ml plasma and after 4 months was 190 ng/ml. These findings suggest that more than 4 weeks are necessary to achieve a steady state condition. Avioli and Haddad (1973) reported a similarly slow rise in plasma 25-OHD\(_3\) levels upon feeding a normal adult 40,000 IU (about 650 IU/kg) vitamin D\(_3\) daily for 3 weeks. No significant increase from the base line level of 14-15 ng/ml occurred during the first week of vitamin D\(_3\) supplementation. The concentration gradually increased to approximately 90 ng/ml. After vitamin administration was discontinued, the plasma 25-OHD\(_3\) level slowly declined, dropping to the half-peak level (45 ng/ml) in 4-5 weeks.

IV. TOXICITY

High levels of 25-OHD have been found in all cases of hyperparathyroidism in which this metabolite was determined. Hughes et al. (1976) studied two patients suffering from osteomalacia, who were receiving 50,000 and 250,000 IU vitamin D\(_2\) (about 750 and 3500 IU/kg body weight) daily (duration of treatment was not stated), and who had exhibited signs of vitamin D toxicity. The 25-OHD\(_2\) levels in these patients were 518 and 592 ng/ml plasma, approximately 15 to 20 times the normal values, and considerably higher than would be predicted from the empirical equation of Stamp et al. (1977). A third patient, suffering from post-surgical hypoparathyroidism, had received 100,000 IU (about 1500 IU/kg) daily for an unspecified period, but had shown no signs of vitamin D intoxication. His serum 25-OHD\(_2\) level, although markedly elevated (319 ng/ml), was lower than the patients with overt toxicity. Davies and Adams (1978) reported serum 25-OHD levels of 400 and 450 ng/ml in two patients showing signs of vitamin D toxicity. One patient had received 150,000 IU (about 2000 IU/kg) vitamin D daily for 7 years, and the other 100,000 IU (about 1500 IU/kg) daily for 10 years. Haddad and Stamp (1974) found levels of 206, 490, and 690 ng/ml serum 25-OHD in three adults whose clinical courses were consistent with vitamin D toxicity. The amount and duration of the vitamin D
treatment were not stated. Preece et al. (1975) treated 14 patients with 50,000–100,000 IU vitamin D₂ (about 750–1500 IU/kg) daily for unspecified periods. In those patients whose serum calcium levels remained within normal limits on this regimen, the mean concentration of 25-OHD was 52.8 ng/ml. Three patients on this dosage developed hypercalcemia and signs of vitamin D intoxication. Their serum 25-OHD concentrations were "between 350 and 525 ng/ml."

Streck et al. (1979) reported persistent hypercalcemia in a woman who had received 100,000 IU vitamin D daily (about 1500 IU/kg) for 4 years. At that time her plasma 25-OHD₃ was 283 ng/ml. Treatment with glucocorticoids reduced serum calcium to normal levels within 10 days but plasma 25-OHD₃ levels remained markedly elevated for more than a year after withdrawal of vitamin therapy.

The development of vitamin D intoxication in a 4-year-old, bilaterally nephrectomized child is of special interest (Counts et al., 1975). The child had received 15,000 IU vitamin D (about 1000 IU/kg) daily for 2 months, followed by 50,000 IU (about 3000 IU/kg) daily for 1 month, and then 100,000 IU (about 6000 IU/kg) daily for an additional 2 months. A marked hypercalcemia developed (serum calcium 17.2 mg/dl), together with vomiting, abdominal pains, and radiographic evidence of subperiosteal resorption. At the time vitamin D therapy was discontinued the serum level of 25-OHD was 635 ng/ml serum, more than 20 times the normal value. The level then fell slowly, to about 300 ng/ml in 10 days and to 100 ng/ml in 3 months. Thus, even 3 months after discontinuance of vitamin D intake, the serum 25-OHD level remained about three times the normal value. Because 1,25-(OH)₂D could not be formed in the absence of renal tissue, these findings suggest that 25-OHD or some unidentified metabolite mediated the toxic response.

The consistently elevated levels of 25-OHD in the blood of patients with hypervitaminosis D have persuaded some investigators that it is the agent causing the intoxication (Counts et al., 1975; Davies and Adams, 1978; Fraser, 1978; Gertner and Domenech, 1977; Hughes et al., 1976). Gertner and Domenech (1977) suggested that vitamin D intoxication occurs at serum or plasma 25-OHD levels of 400–500 ng/ml, although considerably lower levels (130 ng/ml) have been found in two infants with vitamin D toxicity (Haddad and Stamp, 1974; Silver et al., 1978). Hughes et al. (1976) pointed out that 25-OHD concentrations are typically increased about 15-fold in clearly recognizable hypervitaminosis D. Davies and Adams (1978) believed that elevated 25-OHD values are characteristic of vitamin D intoxication.

Although such data suggest that 25-OHD may provide a useful index of vitamin D intoxication, its role remains uncertain. 25-OHD concentrations several times normal values have been reported
in some individuals exhibiting no clear signs of toxicity. Also, persons with sarcoidosis and other types of granulomas may display vitamin D intoxication while receiving usual amounts of vitamin D in the diet and with normal, or even low, levels of serum 25-OHD (Papapoulos et al., 1979; Bell et al., 1979). Furthermore, DeLuca (1979) has recently reported the isolation of a 25-OHD₃ metabolite: 25-OHD₃-26,23-lactone, from the plasma of chicks and rats, which appears "in major proportions in vitamin D intoxication."

The biological activity of this compound has not been determined.

No reports have been found of hypervitaminosis D resulting in normal individuals from diet or exposure to sunlight. The Select Committee (SCOGS, 1978) estimated that infants and preschool children were unlikely to receive more than 200 IU vitamin D/kg body weight/day from food sources. The data of Arnaud et al. (1977) and Stamp et al. (1977) suggest that the maximum intake of infants and children from food, summer sunlight, and customary pediatric vitamin supplementation would not exceed 400 IU/kg/day. Similarly, adults are unlikely to receive more than 150 IU/kg vitamin D/day from food sources (SCOGS, 1978), or to synthesize more than 150 IU/kg/day from exposure to sunlight (based on estimates for lifeguards in midsummer by Haddad and Chyu, 1971).

Overt signs of toxicity have been reported in some individuals after long-term administration of 1000 IU or more of vitamin D/kg/day (SCOGS, 1978). To achieve these levels, adults would have to receive large amounts of vitamin D from supplementary sources as well as generous amounts from food and sunlight. Most vitamin D-containing supplements intended for adults contain 400 IU/capsule or less. However, a few contain up to 1000 IU/capsule (Physicians' Desk Reference, 1979) and products are reportedly available which contain even larger amounts. To obtain sufficient vitamin D supplement to reach the toxic level of 1000 IU/kg, a 60-kg adult would need to consume daily, and for extended periods, more than 40 capsules containing 1000 IU; or more than 100 capsules containing 400 IU, in addition to plentiful amounts from food or sunlight. Thus, except in unusual cases it seems unlikely that this level would be exceeded from self medication with over-the-counter preparations.

Small children and especially infants would seem more vulnerable to supplementary vitamin D. Pediatric supplements generally contain 400 IU/capsule or dose. An intake of 1000 IU/kg by a 20-kg child would require the ingestion of 30 or more doses/day in addition to the vitamin D obtained from food and sunlight. Continued intake of this quantity seems unlikely. However, 8 to 12 supplemental doses to a 5-kg infant would approach this toxic level. An overzealous mother providing generous supplements at each feeding might conceivably provide this amount.
In summary, the maximal safe and the minimal toxic doses for vitamin D appear to be in the range of 200-1000 IU/kg/day. Data on the potential long-term deleterious effects of intakes within this broad range are virtually nonexistent and are urgently needed for proper nutritional and clinical management (SCOGS, 1978). Some individuals, particularly infants and small children, may already be approaching the lower limit of this range. There is a paucity of clinical observation or metabolic data on the effects of prolonged use of vitamin D supplements or preferential consumption of vitamin D-rich foods. Since 400 IU/day are adequate for all ages and are generally available through normal diet containing acceptable levels of vitamin D-fortified foods and exposure to sunshine, it would be prudent to avoid any supplementation not prescribed by a physician. Similar prudence suggests that capsules or other supplements should contain no more than 400 IU/dose.

The rapidly evolving elucidation of vitamin D metabolism, together with the development of sensitive analytical tools, should lead to a more precise definition of normal as well as potentially hazardous ranges of vitamin D intake.
V. CONCLUSION

Scientific and medical authorities agree that intakes of 400 IU (10 μg) vitamin D/day are adequate for persons of all ages. There is no evidence of physiologic or nutritional benefit from larger amounts. Because ingestion of high levels for extended periods may cause adverse health effects, total intake in excess of 400 IU/day is unnecessary and may involve long-term risks.

It is not possible to establish a maximum safe dose of vitamin D on the basis of currently available data. Vitamin D intoxication has been reported with daily doses for extended periods of 1000-3000 IU/kg body weight/day (about 5000-15,000 IU/day for infants; 50,000-200,000 IU/day for adults). Additional information is especially needed to evaluate the possible toxic effects of doses between 200-1000 IU/kg/day (about 1000-5000 IU/day for infants; 10,000-60,000 IU/day for adults).

Vitamin D is converted to 25-hydroxyvitamin D (25-OHD) in the liver and then to 1,25-dihydroxyvitamin D (1,25-(OH)$_2$D) in the kidney. 25-OHD is the major circulating metabolite and 1,25-(OH)$_2$D, the most active form. Blood levels of 25-OHD increase in roughly linear fashion with vitamin D intake and are greatly increased in vitamin D intoxication, often 15 to 20 times those of normal individuals. Although some evidence suggests that this compound may be the toxic principle in hypervitaminosis D, other metabolites are also suspected. At this time the issue remains unresolved.

The use of vitamin D supplements by ostensibly normal adolescents and adults is unlikely to increase vitamin D intake to levels which are known to produce hypervitaminosis D (1000-3000 IU/kg/day). However, some individuals may be sensitive to supplementation at lower levels (200-1000 IU/kg/day) and this level may be reached with overly generous supplementation, especially in infants and small children. The use of vitamin D supplements by infants and children should not be necessary if dietary intake is adequate. If supplementation is deemed necessary, the dosage and duration should be prescribed by a physician.

Because 400 IU/day are adequate for persons of all ages, there is little scientific justification for nonprescription capsules or supplements containing more than this amount.

Available sensitive, analytical techniques for various vitamin D metabolites should be utilized to develop objective criteria for vitamin D toxicity. Studies relating vitamin D intake, blood metabolites, serum calcium, and clinical findings may allow a more precise definition of the safe range of vitamin D intake than is now possible.
VI. REFERENCES


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