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Vitamin D: Still a topical matter in children and adolescents. A position paper by the Committee on Nutrition of the French Society of Paediatrics[☆]

La vitamine D : une vitamine toujours d'actualité chez l'enfant et l'adolescent. Mise au point par le Comité de nutrition de la Société française de pédiatrie

M. Vidailhet^{a,*}, E. Mallet^b, A. Bocquet^c, J.-L. Bresson^d, A. Briend^e, J.-P. Chouraqui^f, D. Darmaun^g, C. Dupont^h, M.-L. Frelut^h, J. Ghisolfiⁱ, J.-P. Girardet^h, O. Goulet^d, R. Hankard^j, D. Rieu^k, U. Simeoni^l, D. Turck^{m,*}, Comité de nutrition de la Société française de pédiatrie

^a Service de pédiatrie et génétique clinique, hôpital d'enfants, université Henri-Poincaré, allée du Morvan, 54511 Vandœuvre-les-Nancy, France

^b Université de Rouen, 76183 Rouen, France

^c Cabinet de pédiatrie, CHU de Besançon, 25030 Besançon, France

^d Université Paris-Descartes, 75015 Paris, France

^e Institut de recherche sur le développement, 13572 Marseille, France

^f Université Joseph-Fourier, 38042 Grenoble, France

^g Université Nantes-Atlantique, 44035 Nantes, France

^h Université Pierre-et-Marie-Curie, 75005 Paris, France

ⁱ Université Paul-Sabatier, 31062 Toulouse, France

^j Université de Poitiers, 86034 Poitiers, France

^k Université de Montpellier 1, 34060 Montpellier, France

^l Université de Marseille, 13005 Marseille, France

^m Université Lille Nord de France, 59000 Lille, France

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Summary

The aims of the present position paper by the Committee on Nutrition of the French Society of Paediatrics were to summarize the recently published data on vitamin D in infants, children and adolescents, i.e., on metabolism, physiological effects, and requirements and to make recommendations on supplementation after careful review of the evidence. Scientific evidence indicates that calcium and vitamin D play key roles in bone health. The current evidence, limited to observational studies, however, does not support other benefits for vitamin D. More targeted research should continue, especially interventional studies. In the absence of any underlying risk of vitamin D deficiency, the recommendations are as follows: pregnant women: a single dose of 80,000 to 100,000 IU at the beginning of the 7th month of pregnancy; breastfed infants: 1000 to 1200 IU/day;

Résumé

L'objectif de cette mise au point du Comité de nutrition de la Société française de pédiatrie est de résumer les connaissances récemment acquises chez l'enfant et l'adolescent et de proposer des recommandations de prescription. En l'absence de risque particulier, les recommandations sont les suivantes : femme enceinte : dose de charge unique de 80 000 à 100 000 UI au début du 7^e mois de grossesse ; nourrisson allaité : 1000 à 1200 UI/j ; enfant moins de 18 mois, recevant un lait enrichi en vitamine D : complément de 600 à 800 UI/j ; enfant moins de 18 mois recevant un lait de vache non enrichi en vitamine D : 1000 à 1200 UI/j ; enfant de 18 mois à 5 ans et adolescent de 10 à 18 ans : 2 doses de charge trimestrielle de 80 000 à 100 000 UI en hiver (novembre et février). En présence d'un risque particulier (forte pigmentation cutanée ; absence d'exposition

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* Corresponding authors.
e-mail : michel.vidailhet@wanadoo.fr

children less than 18 months of age, receiving milk supplemented with vitamin D: an additional daily dose of 600 to 800 IU; children less than 18 months of age receiving milk not supplemented with vitamin D: daily dose of 1000 to 1200 IU; children from 18 months to 5 years of age: 2 doses of 80,000 to 100,000 IU every winter (November and February). In the presence of an underlying risk of vitamin D deficiency (dark skin; lack of exposure of the skin to ultraviolet B [UVB] radiation from sunshine in summer; skin disease responsible for decreased exposure of the skin to UVB radiation from sunshine in summer; wearing skin-covering clothes in summer; intestinal malabsorption or maldigestion; cholestasis; renal insufficiency; nephrotic syndrome; drugs [rifampicin; antiepileptic treatment: phenobarbital, phenytoin]; obesity; vegan diet), it may be justified to start vitamin D supplementation in winter in children 5 to 10 years of age as well as to maintain supplementation of vitamin D every 3 months all year long in children 1 to 10 years of age and in adolescents. In some pathological conditions, doses of vitamin D can be increased. If necessary, the determination of 25(OH) vitamin D serum concentration will help determine the level of vitamin D supplementation.

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1. Introduction

Vitamin D, or calciferol, is not strictly speaking a vitamin, but rather a pre-pro-hormone, physiologically synthesized in the epidermis from its precursor, 7-dehydrocholesterol, under the effect of ultraviolet B (UVB) radiation. The objectives of this position paper by the Committee on Nutrition of the French Society of Paediatrics (CNSFP) are to summarize the recently acquired knowledge on vitamin D in children and adolescents and to make recommendations for vitamin D prescription for pregnant women, infants born at term, children, and adolescents in light of recent evidence on the estimation of vitamin D requirements. Only the bone and phosphocalcic aspects will be discussed, excluding extraosseous diseases for which general reviews have recently been published [1–4], including 1 in the *Archives de Pédiatrie* in 2010 [2]. Given the current uncertainty as to the causal relationship between vitamin D deficiency and diseases independent of phosphocalcic metabolism, these were not taken into consideration in these guidelines.

2. Review of the physiological factors

Two forms of vitamin D exist:

- ergocalciferol, or vitamin D₂, originates from plants, for the most part industrially produced by exposing the ergosterol present in yeasts to UVB radiation;
- cholecalciferol, or vitamin D₃, is the natural form produced by cutaneous photosynthesis or dietary intake of animal

au soleil estival ; affection dermatologique empêchant cette exposition ; port de vêtements très couvrants en période estivale ; malabsorption digestive, cholestase, insuffisance rénale, syndrome néphrotique ; certains traitements [rifampicine ; traitement anti-épileptique: phénobarbital, phénytoïne] ; obésité ; régime aberrant [végétalisme]), il peut être justifié de poursuivre la supplémentation toute l'année chez l'enfant de 1 à 5 ans et chez l'adolescent, et de la maintenir entre 5 et 10 ans. Dans certaines situations pathologiques, les doses peuvent être augmentées. Si nécessaire, le dosage de la 25(OH) vitamine D guidera la prescription de vitamine D.

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products, essentially fatty fish (*fig. 1, table I*). The contribution of oil fortified in vitamin D is insignificant.

The main metabolic pathway comprises 2 successive stages of hydroxylation, metabolizing to 1.25-dihydroxyvitamin D [1.25(OH)₂D, or calcitriol], the only active metabolite:

- the first hydroxylation in the liver, leads, through very active and little-regulated 25 hydroxylase, to 25-hydroxyvitamin D [25(OH)D], or calcidiol (a pro-hormone), the best circulating marker of vitamin status and reserves given its very high affinity for vitamin D binding protein (DBP) and its long half-life (3 weeks). In addition to the liver, adipose tissues also store vitamin D, but the contribution of vitamin D, stored in adipocytes, to its physiological regulation remains poorly known. It seems sequestered rather than stored in fatty tissue, with an excess of fat mass limiting the effects of vitamin D intake and, on the contrary, lipolysis being accompanied by an increase of circulating calcidiol;
- the 2nd hydroxylation, via 1- α -hydroxylase of the proximal renal tubule, is, in contrast, closely regulated; it leads to calcitriol, which has hormone properties. It has a half-life of a few hours and its blood concentration is 1000 times lower than that of 25(OH)D. Calcitriol plays a vital role in maintaining the body's phosphocalcic content by increasing the intestinal absorption of calcium (Ca) and phosphorus (P), and the renal tubule reabsorption of Ca, ensuring a sufficient phosphocalcic product (PO₄ × Ca) for adequate mineralization of bone tissue. Calcitriol stimulates the secretion of a number of proteins via osteoblasts (osteocalcin, osteopontin, osteonectin, type I collagen, RANK ligand, etc.) and differentiation of

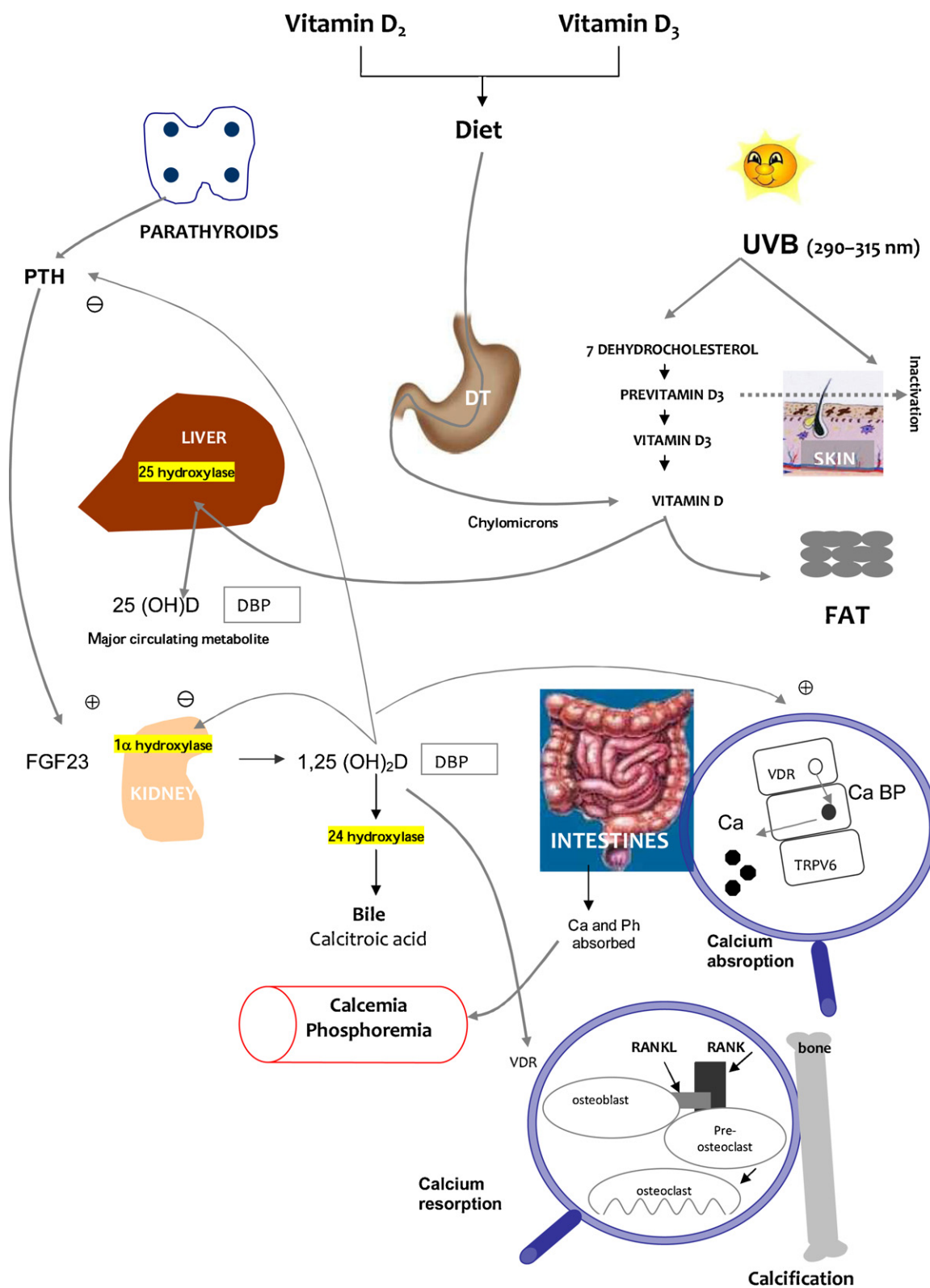


Figure 1. Diagram of vitamin D metabolism and its functions in phosphocalcic metabolism and bone mineralization. The functions independent of bone metabolism are not shown (see text) [4]. UVB: ultraviolet B rays; PTH: parathormone; DT: digestive tube; DBP: D binding protein VDR: vitamin D receptor; FGF: fibroblast growth factor; Ca: calcium; Ph: phosphorus; Ca BP: calcium binding proteins; TRPV6: transient receptor potential cation channel, family V, member 6.

Table 1
Equivalences, abbreviations, and synonyms.

Equivalences	Abbreviations and synonyms
<i>Vitamin D</i>	
1 μg = 2.5 nmol	25 hydroxyvitamin D = 25(OH)D = calcidiol
1 μg = 40 IU	1–25 dihydroxyvitamin D = 1.25(OH) ₂ D = calcitriol
<i>Plasma 25(OH)D</i>	
1 ng/mL = 2.5 nmol/L	Vitamin D = Calciferol Vitamin D ₃ = Cholecalciferol Vitamin D ₂ = Ergocalciferol

myelomonocytic precursors into osteoclasts. The production of calcitriol is regulated by parathormone (PTH), phosphor-emia, and calcemia, and inhibited by fibroblast growth factor 23 (FGF 23) and calcitriol itself. Its inactivation begins by activation of 24-hydroxylase, which ends in inactive 24-25(OH) metabolites [3–5].

A number of general review articles have reviewed vitamin D over the past few years [1–8], emphasizing its major role in phosphocalcic homeostasis and bone health as well as a series of actions involving it in cell differentiation, proliferation and apoptosis, immunomodulation, insulin secretion, and renin renal production. These multiple actions are made possible by the presence of vitamin D receptors (VDRs) in most tissues and by a 1 α -hydroxylase activity in certain organs and cells outside the kidney (e.g., placenta, lymphoid tissue, breast, colon, prostate, keratinocytes, and macrophages), allowing local synthesis of calcitriol for autocrine or paracrine actions. Calcitriol regulates several genes, directly or indirectly. Many studies, for the most part observational, have suggested a protective role against certain cancers (colorectal, breast, prostate) as well as infectious (tuberculosis, viral infections), autoimmune (psoriasis, multiple sclerosis, lupus, type I diabetes), and cardiovascular diseases. In children, studies suggest a preventive effect against type 1 diabetes [9], episodes of wheezing [10], and acute respiratory infections [11], but the level of evidence remains insufficient to confirm these actions, independent of phosphocalcic metabolism.

3. Historical review

After the description of rickets by Whistler (1645) and Glisson (1650), the efficacy of cod liver oil was shown by Percival in 1782, and Trousseau underscored (1861–1867) its preventive and curative efficacy [12,13]. At the time of the Industrial Revolution, rickets was very frequent in the large cities of Europe and North America, affecting, for example, 80% of young children in Boston [12,13]. As early as 1822, Sniadecki contrasted the frequency of the disease in the center of Warsaw and its rarity in the surrounding countryside, highlighting the role of lack of sun

exposure. The role played by ultraviolet (UV) rays was demonstrated by Huldshinsky as well as Hess and Weinstock, who determined the effective wavelengths (UVB: 290–315 nm) [13]. The apparent contradiction between the respective roles played by sun exposure and a dietary factor present in fish oil was resolved by Steenbock and Black, who demonstrated that UVB transformed a precursor present in the skin and food into vitamin D [13]. Even before vitamins D₃ and D₂ and their respective precursors (7-dehydrocholesterol and ergosterol) had been identified, by comparing infants whose skin was exposed to the sun and who received cod liver oil to controls, in 1926 Eliot demonstrated the remarkable preventive efficacy of these treatments [13]. This led to the decision in the United States to fortify the widely consumed milk in vitamin D₂ beginning in 1934. This supplementation was challenged in Europe by the occurrence in the United Kingdom at the beginning of the 1950s of cases of hypercalcemia due to excessive intake of vitamin D, with the doses administered possibly exceeding 4000 IU/day. In 1976–1977, the European Society of Paediatric Gastro-enterology and Nutrition (ESPGAN) recommended supplementing infant formulas with 40 to 80 IU/100 kcal, a recommendation that was applied in most European countries, except for Finland, France, and countries in Eastern Europe, where it was decided, for safety reasons, to rely on medical supplements. Supplementation is still regulated in France by a ministerial decree published in 1963 and in 1971 [14], following surveys showing a very high prevalence of rickets at the end of the 1950s (17% and 12% of young children hospitalized in Lyon and Marseille, respectively). This supplementation, considered to be safer, corresponds nonetheless to higher intake than milk fortification: 1000 to 1500 IU/day in light-skinned infants depending on sun exposure, 2500 IU/day if the infant's skin is highly pigmented, 1500 IU/day in the premature infant; daily prevention until 18 months of age, during winter from 18 months to 5 years, replaced if necessary by a booster dose 1 to 2 times in winter. The prevalence of rickets significantly decreased but remained excessive in 1.7% of youth hospitalized in Lyon (1984), 0.5% in Rouen (1985), and 0.4% in Nancy (1985), probably because of poor observance of the recommendations. These results were confirmed by 2 surveys, 1 conducted from 1988 to 1990 in the hospitals of 15 French departments, the other in healthy infants 8 to 10 months old, measuring 25(OH)D at the end of winter and summer in 10 cities in metropolitan France [15]. These results led to authorization by ministerial decree published on 13 February 1992 (translating into French law the European Commission Directive of 14 May 1991 on infant formulas and follow-on formulas), of fortifying infant formulas at 40 to 100 IU/100 kcal and follow-on formulas at 40 to 120 IU/100 kcal [16]. This fortification was rapidly followed by the sharp drop in the prevalence of nutritional rickets. It was confirmed with the same fortification in the 2006/141/CE directive of 22 December 2006 passed into French law by the decree of 11 April 2008 [17]. In 2005, a study conducted by e-mail in 16 university hospitals (CHU) in France

showed the near disappearance of nutritional rickets (69 cases in 1991, 40 in 1993, and a single case in 2005). Initially vitamin D₂, easily obtained from UVB-irradiated yeast extracts, was the only supplement used; it is increasingly being replaced by natural vitamin D₃, obtained from lanolin from sheep wool. A lower biological efficacy of vitamin D₂ has often been claimed (30% of the efficacy of vitamin D₃) but remains debated [18]. It is only 40 years after the identification of vitamin D that its activated derivatives were discovered: 25(OH)D (calcidiol), the best marker of vitamin D status, and, in 1971, 1,25(OH)₂D (calcitriol), the only active metabolite and a true hormone [3-5]. Knowledge on 25(OH)D has served to define the thresholds of mild, moderate and severe deficiency, to demonstrate the role played by maternal deficiency in the onset of neonatal hypocalcemia [19], to detail the frequency of deficiency in adolescents [20], and to set the upper limits of supplementation. The role played by certain polymorphisms of the VDR in defective bone mineralization induced by insufficient dairy product intake [21], and the existence of DBP polymorphisms [22] have been demonstrated.

Whereas vitamin D fortification for infants and young children, beginning in 1992, eradicated rickets in France, an inverse phenomenon appeared in the United States and other countries: the resurgence of nutritional rickets, particularly in dark-skinned populations [23,24].

4. Determination of vitamin status

4.1. Vitamin D status marker

Rickets has long remained the only evidence of a vitamin D deficiency. Today, 25(OH)D is the biological marker to assess vitamin D status [1-8,25-27]. This property stems from its very long half-life (3 weeks), its strong affinity for DBP, and its blood concentration, which is 1000 times higher (10 to 55 ng/mL) than for 1,25-(OH)₂D (30 to 50 pg/mL) and 10 times higher than vitamin D itself. The measurement method must be reliable and take into account the 2 fractions: 25(OH)D₃ coming from cutaneous photosynthesis, dietary intake and any supplementation, and 25(OH)D₂, which can only come from supplementation. Certain radioimmunologic methods that do not adequately recognize 25(OH)D₂ have erroneously suggested a vitamin deficiency. Today, laboratories that perform these measurements use quality control such as the DEQAS international control system [7,27].

The determination of the levels of 25(OH)D allowing for a normal phosphocalcic metabolism and bone mineralization require functional markers. Extraosseous diseases cannot be taken into account to set this level without randomized controlled interventional trials (RCITs) establishing a causal relation with vitamin D status [28].

Three functional markers are available today in children and adolescents to set the 25(OH)D threshold to achieve:

- PTH measurement in plasma, combined with 25(OH)D measurement, looking for a 25(OH)D threshold below which the PTH concentration begins to rise. This increase in PTH secretion probably indicates the need to release Ca from bone tissue to maintain calcemia;
- evaluation of the intestinal absorption fraction of Ca at different levels of serum 25(OH)D, using 2 stable isotopes of Ca, 1 administered orally and the other intravenously;
- assessment of bone mineral density (BMD) and bone mineral content (BMC) using dual energy X-ray absorptiometry at different levels of circulating 25(OH)D.

Other markers of bone metabolism such as osseous alkaline phosphatase, osteocalcin, C- and N-terminal telopeptides of type I collagen, and deoxypyridinoline have been shown to be of little value [29].

Measurement of the hormone itself, calcitriol, necessary in some rare diseases, does not reflect vitamin D status because of the very strict control of its synthesis, its very short half-life (4 h), and its very low concentration in serum. When a subject reaches a deficiency in vitamin D, the drop in intestinal absorption of Ca and the transitory drop in circulating ionized Ca lead to an increased secretion of PTH, which very rapidly induces an increased synthesis of calcitriol. In practice, this explains why a vitamin D deficiency, even severe, can be found with a normal or even increased circulating calcitriol concentration [5,12].

4.2. Normal status and deficiency threshold

Before the discovery of the hydroxylated derivatives, the normal level was defined by the absence of any clinical sign of deficiency, rickets in children and osteomalacia in adults. Thereafter, as for many nutrients, the normal range was defined by the mean \pm 2 standard deviations of the 25(OH)D value sampled in a population of healthy subjects, i.e., 25 to 137.5 nmol/L for European and North American populations.

This threshold for defining clinical deficiency seems adequate in children [7,8,12], even if rickets is observed most often below 20 nmol/L [30]. In Europe, very low serum concentrations of 25(OH)D (<25 nmol/L) are very frequently observed in winter and the beginning of spring: in the United Kingdom, approximately 1.5% of children from 1.5 to 3 years of age (27% of children of Asian ancestry), 3% of children 4 to 6 years of age, 4% of boys and 7% of girls from 7 to 10 years of age, 11% of adolescents from 11 to 14 years of age, and 16% of boys and 10% of girls from 15 to 18 years of age [31]. In northern Europe (Denmark, Finland, and Poland), more than one-third of adolescents have 25(OH)D concentrations less than 30 nmol/L in winter [32]. In France, in winter 10 to 40% of children and adolescents have a 25(OH)D concentration less than 25 nmol/L, with an increase in PTH [20,33]. Even in a country with as much sunshine as Greece, 47% of adolescents from 15 to 18 years of age and 14% of those 13 to 14 years of age have, in

winter, a 25(OH)D concentration less than 25 nmol/L [34]. Mallet et al. emphasize the great variability of supplementation in young children, below the recommended levels in the Rouen region and the frequent absence of any supplementation during winter. This results in serum 25(OH)D concentrations less than 25 nmol/L in 6% of children, with, as in the United Kingdom, a drop in 25(OH)D values from 18 months to 6 years of age [35]. A recent French multicenter study confirmed the lack of supplementation in older children: out of 1256 children aged 19 months to 5 years, 53.4% did not have a prescription for vitamin D or had a prescription under the recommended levels [36]. The same does not hold for children under 18 months of age in whom the same study showed that the percentage of insufficient prescriptions, compared to the recommended doses, was only 3.8% [36].

In newborns, whose vitamin status depends entirely on the mother's status, several studies [19,37] have shown a relationship between neonatal hypocalcemia and poor maternal vitamin D status. Recent studies conducted with high-resolution 3-dimensional ultrasound have demonstrated a higher femoral splaying index (FSI) ($FSI = 0.084$) when maternal 25(OH)D serum concentrations were very low (<25 nmol/L), than when this concentration was normal (>50 nmol/L; $FSI = 0.074$). The FSI is at intermediate values (0.078) when the 25(OH)D concentration is between 25 and 50 nmol/L [38]. Several publications have shown the efficacy of preventive maternal supplementation, either daily during the entire pregnancy (400 IU) or a single dose (80,000 or 100,000 IU) given at the beginning of the 7th month of pregnancy [19,37]. In breastfed infants, the absence of vitamin D supplementation, even though it is necessary and should begin during the neonatal period, is considered to be one of the 2 major reasons, along with dark skin pigmentation, of the reappearance of rickets in different countries such as the United Kingdom, the United States, and Canada. Certain healthcare professionals, associations, even the health authorities, seem to consider that breastfeeding, considered as "natural", requires no supplementation. The French ministerial decree, which had not been reviewed since 1971 [14], indicates that supplementation should not begin before 6 weeks of life, even if the child is breastfed, even though the vitamin D concentration in mother's milk is very low, between 8 and 48 IU/L [39]. A breastfeeding mother would need an oral dose of 4000 IU/day, causing her to run the risk of hypervitaminosis, to ensure a sufficient 25(OH)D intake for the breastfed child [40]. Maternal reserves of vitamin D can sustain the infant's requirements during the first 6 weeks of life only if the mother's vitamin D status was sufficient at the end of pregnancy; this is often not the case, particularly when the last trimester of the pregnancy takes place in winter and at the beginning of spring and the mother has not received sufficient supplementation.

In adolescents, symptomatic rickets can be observed in exceptional cases: Mallet et al. [41] compiled 41 cases in 5 years in

several French hospitals, for the most part in adolescent females with dark skin pigmentation and/or who wear skin-covering clothes, while this disease is no longer found in young children beyond 2 years of age, other than deformities related to sequelae [12]. This clearly illustrates how critical the periods of bone growth spurts are in early childhood and adolescence.

4.3. Deficiency thresholds

4.3.1. Adults and the elderly

Several authors consider that the deficiency threshold of 25 or 30 nmol/L is poorly adapted to adults and elderly persons [42–45]. Different studies have even resulted in distinguishing 2 threshold levels above the clinical deficiency threshold: a moderate level at 50 nmol/L and a mild deficiency level at 75 nmol/L. The latter threshold is based on the 25(OH)D serum concentration below which circulating PTH begins to rise according to the studies conducted by Holick et al. [25,42] and Chapuy et al. [45]. Other studies did not confirm this threshold; even if PTH varies inversely to 25(OH)D, the thresholds observed vary from 45 to 125 nmol/L depending on the publication [46]. Similarly, a study reported by Heaney et al. [47] showing that in the adult female the percentage of digestive absorption of Ca rises from 45 to 65% when circulating 25(OH)D increases from 50 to 80 nmol/L, was challenged because of poorly adapted methodology and erroneous interpretation of certain results [46]. On the other hand, other studies show that the intestinal absorption fraction of Ca in the adult [46] reaches its maximum between 30 and 50 nmol/L.

4.3.2. In children and adolescents

In 365 infants and young children, Gordon et al. found the inverse relationship between 25(OH)D and PTH observed in adults: 40% of these children had a serum concentration of 25(OH)D less than 75 nmol/L, 12% a concentration less than 50 nmol/L, with one-third of the latter having radiological signs of rickets [48]. Several publications confirm this inverse 25(OH)D/PTH relationship in children and adolescents [49–52]. According to Cashman [31], the available data could suggest that the mild threshold should be 70 nmol/L. On the other hand, Hill et al. [51] determined a threshold of 60 nmol/L in female adolescents and could not establish a threshold in adolescent males, whereas Esterlé et al. [52], although they also confirmed an inverse PTH/25(OH)D correlation, found a much lower threshold, at 40 nmol/L. Overall, it is not possible to determine a precise 25(OH)D value corresponding to maximal PTH suppression [53]. The functional consequences of PTH variations in a bone growth spurt period such as adolescence may differ from the those in adults. In a study on adolescents at the beginning of puberty (Tanner stage 2) who took Ca supplements, Tylavsky et al. [54] showed that although PTH is negatively correlated with

25(OH)D, it is also, apparently paradoxically, positively correlated with BMD and BMC. Adolescents with a serum concentration of 25(OH)D at the lower limit of the normal range (45 nmol/L) and increased PTH have a better gain in bone surface (+8%) and BMC (+11%) than those with a 25(OH)D concentration at 85 nmol/L. Also, in children and adolescents, Abrams et al. indicated that only a minimal increase of the intestinal Ca absorption coefficient was observed above a 25(OH)D serum concentration of 30 nmol/L [55]. Absorptiometric studies are also used to determine a deficiency threshold at a higher level than the severe clinical deficiency threshold retained for rickets. For diaphyseal cortical bone, Outila et al. [56] and Cashman et al. [57] observed a reduction in BMD for 25(OH)D less than 40 to 45 nmol/L and 50 to 60 nmol/L, respectively. For trabecular bone, however, certain studies did not show defective mineralization [29,57], except for very low 25(OH)D concentrations, less than 20 nmol/L [58]. Esterlé et al. demonstrated that when calcium intake is low (<600 mg/day), BMD and BMC of trabecular bone are significantly decreased and correlated with low 25(OH)D values [52]. Two RCITs, conducted on young adolescent girls, showed a positive effect of vitamin D supplementation on mineralization of the pelvis and the lumbar vertebrae [59,60]. A recent meta-analysis [61] covering only 6 RCITs out of 1653 references analyzed, included 541 adolescents who had received vitamin D supplementation for 3 months compared to 343 controls. This supplementation showed little effect in adolescents with normal serum concentrations of 25(OH)D, but was beneficial in children and adolescents who had low 25(OH)D concentrations (<35 nmol/L), with an increase in BMD in the lumbar vertebrae and in the body's total BMC.

Finally, radiologically documented cases of nutritional rickets have been described in African infants and young children who had serum 25(OH)D concentrations as high as 40 to 45 nmol/L [23]. In Nigerian infants and young children with rickets aged 6 to 36 months, who had very low calcium intake and 25(OH)D concentrations greater than 25 nmol/L, a sharp increase in 1,25(OH)₂D, observed after administration of vitamin D, suggesting an insufficient vitamin D status associated with low calcium intakes [62].

In summary, in children and adolescents, as in adults, the 25(OH) vitamin D serum level of 50 nmol/L could be retained as a threshold for moderate vitamin D deficiency, below which defective mineralization can appear. This threshold should be retained because of the possible (but not demonstrated) increase in the risk of fractures and an excessively low "bone mass peak" at the end of growth as a result of insufficient calcium accretion in bone. This 50-nmol/L threshold is currently retained in North America to determine the recommended dietary allowances (RDA) in vitamin D, i.e., the allowances ensuring good bone health in 97.5% of the population of children and adolescents, provided that intake of other nutrients is adequate, in particular for Ca [46]. Of note,

this 50-nmol/L threshold is also retained in North America for adults up to 70 years of age.

Insufficient vitamin D status is common in winter in Europe, where all the countries are located above 35° latitude north, beyond which photosynthesis of vitamin D falls. The winter season has a longer duration at higher latitudes, lasting from November to February or October to March in metropolitan France, which is located between 42° and 51° latitude north. In northern Europe, a 25(OH)D serum concentration less than 50 nmol/L is found in two-thirds of children during the winter and at the beginning of spring (Denmark, Finland, Poland, and Russia) [32,50]. In Germany, more than 60% of children of German ancestry and more than 75% of children of immigrants aged 3 to 17 years have a 25(OH)D concentration less than 50 nmol/L; from 1 to 3 years, the percentages are lower, about 30% for children of German ancestry and 40% in immigrant children [63]. In France, nearly all adolescents in winter have a serum concentration of 25(OH)D less than 50 nmol/L [33]. In the United Kingdom, 20% of children aged 1.5 to 4 years, 25% of those aged 5 to 10 years, and 40 to 50% of adolescents aged 11 to 18 years have a 25(OH)D concentration lower than 50 nmol/L, exceeding 70% in children of Asian ancestry at 2 years of age [31]. In the United States, 48% of adolescent girls in Maine (the farthest north on the east coast, at 45° latitude) have a 25(OH)D serum concentration lower than 50 nmol/L at the end of winter [64].

5. Vitamin D requirements and recommended nutrient intakes

5.1. In children and adolescents

An exact determination of the oral allowances corresponding to the vitamin D requirements is impossible, because of the remarkable efficiency of cutaneous photosynthesis and its substantial variability depending on season, latitude, altitude, time of day, cloud cover, pollution, the skin surface exposed to the sun, the duration of exposure, pigmentation, and the use of sun screen lotions. **Many arguments suggest that the total intake of vitamin D₃ through photosynthesis and/or orally, should be at least 1000 IU/day in both children and adults [7,43,65,66].**

Taking into account all of the dietary and sun exposure variables, Garabédian et al. [67] proposed a decision graph, which, after assessment in 116 children (excluding those with dark pigmentation or with a disease that may interfere with vitamin D metabolism), was simplified by excluding all the items with a low discriminatory power. Thus simplified, it identified children at risk of wintertime vitamin D severe deficiency with a 25(OH)D serum concentration less than 25 nmol/L. Although this graph can be useful for the healthcare professional examining children in whom the level of sun exposure in summer and the dietary intake of vitamin D-rich

foods such as oily fish can be assessed, it cannot be used for general recommendations.

Until these last few years, vitamin D requirements were limited to preventing rickets. In children younger than 18 months with no or incomplete walking autonomy, the limited outdoor sun exposure and bone growth spurts undoubtedly explained the frequency of rickets, which became much rarer in older children.

To ensure satisfactory bone mineralization in childhood and beyond, today it seems justified to maintain a 25(OH)D serum concentration equal to or greater than 50 nmol/L, but the oral intake required to reach this level remains difficult to determine. In summer, the remarkable efficacy of photosynthesis suffices to maintain 25(OH)D concentrations at a satisfactory level in children old enough to walk who are regularly outdoors with exposure to the sun and who avoid excessively covering clothing. During the winter months, on the other hand, the interruption of cutaneous photosynthesis, the scarcity of foods with natural vitamin D other than oily fish (salmon, herring, sardines, trout, mackerel, in which the vitamin D content varies from 7 to 18 µg/100 g), medical supplementation is required. From 3 to 17 years of age, food intake of vitamin D is very low in France, from 80 ± 52 IU/day in boys and 70 ± 40 IU/day in girls, according to the INCA 2 survey conducted in 2006 [68].

In 2008, the Nutrition Committee of the American Academy of Pediatrics [69], observing that “adequate” intake retained by the American Institute of Medicine (IOM) in 1997 was insufficient, at least in winter, recommended an oral intake of 400 IU/day, which seemed necessary to maintain 25(OH)D serum concentrations at or above 50 nmol/L in children and adolescents. However, the interference of photosynthesis, the imprecision of certain measurement methods, the variability of responses to vitamin D depending on the base level of 25(OH)D, the lack of studies with increasing vitamin D intake, the possibility of a variability in the responses to vitamin D intake depending on whether it was D₂ or D₃, and perhaps different genetic profiles (polymorphisms of the VDR, the DBP genes) have made it impossible to establish a dose–response curve [8].

To eliminate the effect of photosynthesis as completely as possible, the IOM [28,46], responsible for establishing the new North American recommendations, assessed the requirements in vitamin D based on RCITs conducted at very high latitudes of the Northern hemisphere, above 55°N, 3 of which in children and adolescents. Taking into account the total oral intake of vitamin D (basic dietary intake + supplementation in the interventional groups) and using regression analysis after a logarithmic transformation of the vitamin D intakes, these studies showed a dose–effect relation between vitamin D₃ intake and serum 25(OH)D. The absence of a difference between values in children, adolescents, and adults at the same latitudes and at different ages allowed the IOM to group all the data to obtain a predictive

equation and a single “dose–effect” curve that is valid from 6 to 70 years of age. The IOM was thus able to establish 600 IU/day as the recommended dietary allowance (RDA) corresponding to a 25(OH)D serum concentration of 50 nmol/L and the estimated average requirement (EAR) at 400 IU/day corresponding to a 25(OH)D concentration of 40 nmol/L (a value equidistant between the severe deficiency threshold of 25 nmol/L and the value of 50 nmol/L corresponding to the new RDA). At lower latitudes, from 40 to 49°N (comparable to the latitude of metropolitan France), the 25(OH)D serum concentration in winter is 24% higher on average for similar vitamin D intake, which suggests that photosynthesis is less compromised in France than above 50°N. Similarly, only 45% of the variance of 25(OH)D at these latitudes is explained by oral vitamin D intake, whereas this rises to 72% at the highest latitudes above 60°N.

Since this IOM publication, Cashman et al. [70] have published the mid-point interim results of the OPTIFORD project conducted in adolescent girls (mean age, 11.3 years) living at these very high latitudes (Denmark, 55°N, and Finland, 60°N), the first results of a RCIT (0, 200, and 400 IU/day supplementation), with measurement of 25(OH)D at the beginning of autumn (September and October) and at the end of winter (March and April) after 6 months of supplementation. They observed a dose-dependent increase in the serum concentration of 25(OH)D: 2.43 nmol/L per µg of vitamin D₃ intake. The vitamin D₃ intake required to maintain a 25(OH)D concentration higher than 25, 37.5, and 50 nmol/L in 97.5% of these adolescent girls is 330, 540, and 750 IU/day, respectively. They concluded on an EAR slightly lower than that retained by the IOM (250 versus 400 IU/day) and slightly higher RDAs (750 versus 600 IU/day). To explain these differences, the authors emphasize that the values retained by the IOM were based on the mean values of 9 different studies in subjects whose age varied from 6 to more than 60 years and that the curve obtained presents a certain degree of uncertainty, according to the IOM itself.

5.2. In exclusively breastfed infants

The experience accumulated over nearly 20 years has shown the validity of maintaining the previous French recommendations (800 to 1000 IU/day) in the 2001 edition, after the 1992 systematic fortification in vitamin D of infant formulas. These intakes are higher than those recommended throughout Europe and North America (table II). The closely followed practice in France of systematically supplementing breastfed children with 1000 IU/day, because of the low vitamin D content in human milk, has probably contributed to preventing a resurgence of rickets comparable to what has been observed in several Anglo-Saxon countries.

The study reported by Vervel et al. [71] evaluated the effect of vitamin D₂ supplementation with 500 or 1000 IU/day in infants aged 1 to 4 months fed with formulas that were (or

Table II
Examples of recommended vitamin D allowances ($\mu\text{g/day}$) at different ages in 13 European and North American countries.

Year	Country	3 months	9 months	5 years	10 years	15 years	Adults
2004	Germany + Austria + Switzerland	10 (400 UI)	10 (400 UI)	5 (200 UI)	5 (200 UI)	5 (200 UI)	5 (200 UI)
2009	Belgium	10	10	10	10	10–15	10–15
2007	Spain	10	10	10	5	5	5
2001	France	20–25 (800–1000 UI)	20–25 (800–1000 UI)	5	5	5	5
1996	Italy	10	17.5	5	5	7.5	5
2004	Denmark + Finland + Sweden	10	10	7.5	7.5	7.5	7.5
1991	United Kingdom	8.5	7	0 (§)	0 (§)	0 (§)	0 (§)
2010	United States + Canada	10 (400 UI)	10 (400 UI)	15 (600 UI)	15 (600 UI)	15 (600 UI)	15 (600 UI)

(§): 10 $\mu\text{g/day}$ in cases of insufficient UVB exposure.

were not) fortified in vitamin D. In winter, the infants receiving medical supplementation (1000 IU/day) associated with fortified formula had a higher but non-significant serum concentration of 25(OH)D, compared to infants receiving non-fortified formula and the same medical supplementation (85 ± 32 versus 72 ± 22 nmol/L). In the 2nd part, this study showed that if infants fed with fortified formula receive a daily complement of 500 or 1000 IU of vitamin D, their serum concentration of 25(OH)D varies little in relation to the dose received and never exceeds 92.5 nmol/L, including in summer.

5.3. In infants and young children after dietary diversification and reduction of milk intake

In the child fed with vitamin D-fortified milk, in absence of drug supplementation, vitamin D intake decreases from 340 to 400 IU/day in the first 6 months to 230 to 330 IU/day from 6 to 12 months. The reduction of intake is particularly sharp in the 1- to 3-year-old age group, with the frequent change to cow's milk: 180 IU/day from 13 to 18 months, 100 IU/day from 19 to 24 months, 80 IU/day from 25 to 30 months, and 50 IU/day from 31 to 36 months [72]. If only young children continuing to consume vitamin D-fortified milk are considered (vitamin-fortified milk) with at least 250 mL/day, vitamin D intake is higher, 280 IU/day versus 32 IU/day for those who receive non-fortified milks, but it remains under the 2001 French recommended intake [73].

A major problem, difficult to solve effectively, resides in the very poor application of the recommendations after the age of 18 months, which seems to have worsened since the near disappearance of nutritional rickets, giving healthcare professionals and families a mistaken sense of security. In 2005, Mallet et al. emphasized this poor observance in the Haute-Normandie region [35]. This was confirmed by a recent multi-center study showing that 53.4% of French children between 18 months and 5 years of age did not receive the recommended supplementation [36].

The recently published North American Dietary Reference Intakes (DRI) [46] mark a decisive break from those that had been retained as the "adequate intakes" in 1997. EARs are henceforth at 400 IU/day and the RDA at 600 IU/day, for

all ages, from 1 to 70 years, i.e., values 3 times higher than the adequate intake that had been retained by the IOM in 1997. From birth to 1 year, the adequate intakes (AI) retained today are 400 IU/day, twice as high as in 1997.

6. Tolerable upper intake levels

6.1. In adults and adolescents

As shown by the example of lifeguards working all year long in a tropical zone, hypervitaminosis D cannot be caused by sun exposure, even when it is extensive. A cutaneous self-regulation exists with conversion of previtamin D₃ and vitamin D₃ itself into inactive metabolites. The 25(OH)D serum concentration that can be reached in lifeguards does not exceed 250 to 300 nmol/L [25,66,74] and there is no manifestation of hypervitaminosis D (hypercalcemia, hypercalciuria, or renal lithiasis). For Holick [25], the tolerable upper intake (UL) limit could be set at 250 nmol/L, particularly since no case of hypervitaminosis D has been observed below a 25(OH)D concentration of 375 to 500 nmol/L [75,76]. Vieth estimated the intake limit that should not be exceeded in adults undergoing long-term administration at 20,000 IU/day [66]. In 2006, the European Food Safety Authority (EFSA) maintained the UL at 2000 IU/day, i.e., half the non-observed adverse effect level (NOAEL), estimated at 4000 IU/day, judged to correspond to a 25(OH)D serum concentration of 200 nmol/L [39]. The IOM today retains a UL at 4000 IU/day beginning at the age of 9 years, twice as high as that proposed by the EFSA in 2006 and by the same institute in 1997 [46].

6.2. In pre-pubescent children and infants

The epidemic of hypercalcemia cases that occurred in the United Kingdom at the beginning of the 1950s, caused by excessive vitamin D intake that sometimes exceeded 4000 IU/day, and the description of cases of hypercalcemia in young children in East Germany who had received vitamin D prophylaxis in single doses of 600,000 IU repeated every 4 to 5 months (6 doses of 600,000 IU between 0 and 18 months), suggest a UL below 4000 IU/day, which in children should not be exceeded in cases of preventive use of single

Table III

Supplements with D₂ or D₃ [excluding hydroxylated derivatives (25, 1 and 1-25 hydroxy vitamin D) which play no role in the prevention and treatment of nutritional rickets and products administered parenterally].

Vitamin D₃ (cholecalciferol)	Vitamin D₂ (ergocalciferol)
<i>With no association</i>	
Daily prophylaxis ZYMA D [®] : 300 IU/drop	STEROYL [®] : 400 IU/drop UVESTEROL D [®] : 800, 1000, or 1500 IU/dose
Periodic prophylaxis UVEDOSE [®] : 100,000 IU/ampoule D ₃ BON [®] : 200,000 IU/ampoule ZYMA D [®] : 80,000, 200,000 IU/ampoule	Stérogyl 15 A [®] : 600,000 IU/ampoule ^a
<i>In association</i>	
with fluoride ZYMA-DUO [®] : 150 IU/drop and 300 IU/drop FLUOSTEROL [®] : 800 IU/dose	
with calcium 12 different specialties ^b including 200 to 880 IU/tablet or packet	Frubiose Vit D ^{®b} : 1000 IU/ampoule
with other vitamins	UVESTEROL "ADEC" ^{®c} : 1000 IU/mL ^c

IU: international units.

In capital letters: the most widely used agents for nutritional rickets prophylaxis.

^a Cannot be used in children because of excessive per unit concentration.

^b For adolescents and osteoporosis treatment in adults.

^c Designed for premature infants until their theoretical term.

100,000-IU doses, repeated every 3 months in winter (for a total of 2 doses) [77].

In 2006 the EFSA [39] retained a UL of 1000 IU/day from 0 to 10 years and 2000 IU/day beginning at 11 years of age.

For the IOM, this UL should evolve with age [46]: 1000 IU/day from 0 to 6 months, 1500 IU/day from 6 to 12 months, 2500 IU/day from 1 to 3 years, 3000 IU/day from 4 to 8 years, and a value identical to the adult value (4000 IU/day) beginning at 9 years of age.

7. Recommendations

7.1. Background

Today there is consensus on the 30- and 50-nmol/L thresholds to define the 25(OH)D serum values indicating, respectively, severe (with a higher risk of rickets) and moderate (with a higher risk of insufficient bone mineralization and possibly extrasosseous disease) deficiencies. Contrary to what has been accepted by many authors in adults [1,25,43,44,66], a mild deficiency threshold is not retained for children (75 nmol/L) below which bone health may already be threatened and where the risk of diseases independent of the phosphocalcic metabolism may be increased.

The oral vitamin D intake necessary to ensure 25(OH)D serum concentrations at 50 nmol/L or above in winter is still being debated. In absence of cutaneous photosynthesis, according

to interventional studies conducted above 55° latitude (such as Denmark and Finland), the IOM has retained recommended intake of 600 IU/day at all ages from 1 to 70 years. However, for many vitamin D specialists, these recommendations may be insufficient to maintain 25(OH)D serum levels at 50 nmol/L or above [40].

In these conditions, today it is preferable to maintain the recommendations retained in France for more than 20 years [4,5,12,20,36,71], corresponding to 1000 IU/day for the supplementation periods, i.e., all year in children under 18 months and certain children with an underlying risk and during the 6 months of winter in children 18 months to 5 years and in adolescents, retaining for them the single 80,000- or 100,000-IU doses every 3 months so as to improve observance of preventive supplementation. In adolescents, this dose every 3 months in winter can even be replaced by a single 200,000-IU dose when the risk of forgetting the 2nd dose seems high [78].

In children from 5 to 10 years of age, the absence of data on vitamin D status in France during winter does not currently warrant recommending systematic supplementation. A clinical study to be conducted during winter 2011 to 2012 should provide a response for this age group.

Today efforts should be concentrated on the observance of these recommendations, taking into account the galenic forms on the market (table III). Vitamin D₃ will be preferred over vitamin D₂, which seems less active.

7.2. In practice

7.2.1. In individuals with no underlying risk

Recommendations are as follows (*table III*):

- in pregnant women: 1 80,000- or 100,000-IU dose, at the beginning of the 7th month of pregnancy;
- in breastfed infants: 1000 to 1200 IU/day throughout breastfeeding;
- in children under 18 months of age consuming milk fortified in vitamin D₃: add an additional 600 to 800 IU/day;
- in children under 18 months of age consuming cow's milk that is not fortified with vitamin D₃: 1000 to 1200 IU/day;
- in children 18 months to 5 years old: 2 80,000- or 100,000-IU doses in winter, 1 in November, the other in February;
- in adolescents from 10 to 18 years old: 2 80,000- or 100,000-IU doses in winter, 1 in November, the other in February, which can be replaced by a single 200,000-IU dose when the risk of forgetting the 2nd dose seems high.

7.2.2. In individuals with underlying risks

Certain cases warrant continuing supplementation all year long in children aged 1 to 5 years and in adolescents and maintaining it from 5 to 10 years. In certain pathological situations, the doses can be increased. If necessary, measurement of 25(OH)D levels will guide the prescription of vitamin D.

These underlying risks are the following:

- dark skin pigmentation;
- absence of summer sun exposure, a dermatological condition preventing such exposure, wearing skin-concealing clothing in summer;
- malabsorption, cholestasis, kidney failure, nephrotic syndrome;
- certain medical treatments (rifampicin; antiepileptic treatment: phenobarbital, phenytoin);
- obesity;
- children on certain extreme diets (veganism).

8. Conclusion

Systematic fortification of milks designed for infants and young children has led to the nearly total disappearance of nutritional rickets in France since 1992. Better knowledge of vitamin D requirements today shows the importance of maintaining circulating 25(OH)D serum concentrations at a level equal to or greater than 50 nmol/L to ensure satisfactory bone mineralization. In 2010 in North America, the recommended allowance was increased from 200 to 600 IU/day from 1 to 70 years of age. In France, some official recommendations, such as the 1971 ministerial decree and the vitamin D French RDA published in 2001, should be updated. With the recommendations currently proposed

here, supplementation for pregnant women on the one hand, and on the other hand supplementation of all children up to the age of 18 months, and winter supplementation from 1 to 5 years and during adolescence, a satisfactory vitamin D status can be obtained provided there is good observance of the recommendations. Although pursuing supplementation between 5 and 10 years of age seems reasonable and risk-free, clinical studies are lacking today to validate this practice in France.

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