

SCIENTIFIC OPINION

Scientific Opinion on the Tolerable Upper Intake Level of vitamin D¹

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)^{2, 3}

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ABSTRACT

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to re-evaluate the safety in use of vitamin D and to provide, if necessary, revised Tolerable Upper Intake Levels (ULs) of vitamin D for all relevant population groups. The ULs for adults including pregnant and lactating women, children and adolescents were revised. For adults, hypercalcaemia was selected as the indicator of toxicity. In two studies in men, intakes between 234 and 275 µg/day were not associated with hypercalcaemia, and a no observed adverse effect level (NOAEL) of 250 µg/day was established. Taking into account uncertainties associated with these studies, the UL for adults including pregnant and lactating women was set at 100 µg/day. Despite a continuing paucity of data for high vitamin D intakes in children and adolescents, the UL was adapted to 100 µg/day for ages 11-17 years, considering that owing to phases of rapid bone formation and growth this age group is unlikely to have a lower tolerance for vitamin D compared to adults. The same applies also to children aged 1-10 years, but taking into account their smaller body size, a UL of 50 µg/day is proposed. For infants, the UL of 25 µg/day based on previously available data relating high vitamin D intakes to impaired growth and hypercalcaemia was retained as limited additional evidence has emerged since the previous risk assessment. Data on vitamin D intakes from surveys in 14 European countries indicate that intakes in high consumers are below the revised ULs for vitamin D for all population groups. © European Food Safety Authority, 2012

KEY WORDS

Vitamin D, supplements, hypercalcaemia, UL, safety.

¹ On request from the European Commission, Question No EFSA-Q-2011-00955, adopted on 26 June 2012.

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³ Acknowledgement: The Panel wishes to thank the members of the Working Group on Upper Levels: Albert Flynn, Ambroise Martin, Hildegard Przyrembel and Sean (J.J.) Strain for the preparatory work on this scientific opinion and EFSA staff: Anja Brønstrup for the support provided to this scientific opinion.

SUMMARY

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to re-evaluate the safety in use of vitamin D and to provide, if necessary, revised Tolerable Upper Intake Levels (ULs) of vitamin D for all relevant population groups.

Vitamin D derives from the diet but can also be synthesised in the skin under the influence of UV-B radiation. Serum 25(OH)D concentration is a good marker of vitamin D status, but can only be used as a biomarker of vitamin D intake in people with low exposure to sunlight. Following ingestion of large doses of vitamin D, the concentration of 25(OH)D in serum increases, while that of the active metabolite 1,25(OH)₂D is unchanged or even reduced. Very high serum 25(OH)D concentrations may lead to hypercalcaemia, which is considered the critical effect of excess intake of vitamin D. Hypercalciuria can be associated with hypercalcaemia, but it can also occur without.

For the derivation of the UL, the occurrence of hypercalcaemia and hypercalciuria has been assessed in studies using daily or weekly supplementation of vitamin D for several weeks to months. The shorter-term studies were generally performed in seasons of low sun exposure. Study populations were not generally vitamin D-deficient, and two studies were conducted in subjects with a high vitamin D status at baseline. Study populations included whites, African Americans, young men, pre- and postmenopausal women, elderly nursing home residents, and overweight and obese adults. It was concluded that vitamin D at doses up to 275 µg/day does not lead to persisting hypercalcaemia or hypercalciuria in adults.

Long-term health outcomes (all-cause mortality, cardiovascular disease, cancer, fractures and kidney stones) were also considered, but no studies reported an association between vitamin D intake and increased risk for adverse long-term health outcomes. Studies reporting on an association between 25(OH)D concentration and all-cause mortality or cancer were inconsistent. When 25(OH)D concentrations were associated with an increased risk for adverse long-term health outcomes in some studies, there was a wide variation in 25(OH)D concentrations associated with the adverse effect. It was considered that 25(OH)D concentrations cannot be used to characterise the risk for adverse long-term health outcomes.

In adults, a daily vitamin D dose of 250 µg/day (range 234-275 µg/day) was considered to reflect a no observed adverse effect level (NOAEL). This value was based on only two studies of short duration (up to five months) in small samples of healthy young men with minimal sun exposure. To take into account the uncertainties associated with this value, an uncertainty factor of 2.5 was chosen, and the UL was established at 100 µg/day. It was considered that the UL of 100 µg/day for adults also applies to pregnant and lactating women. This UL is supported by two studies in pregnant and lactating women, both using doses of vitamin D₂ or D₃ up to 100 µg/day for several weeks to months, which did not report adverse events for either the mothers or their offspring.

For infants, there is historical evidence on retarded growth from a study in which infants received various regimens of vitamin D exceeding 45 µg/day up to one year of age, although another small study using doses up to 54 µg vitamin D/day until about five months of age did not show such an effect. More recent intervention studies using doses up to 25 µg vitamin D/day (plus the amount ingested via fortified infant formula) for up to five months after birth did not indicate that these intakes are associated with hypercalcaemia in infants. As new data from intervention studies in healthy infants have not become available since the previous risk assessment by the SCF (2003), it was decided that the UL of 25 µg vitamin D/day previously derived for infants from 0 to 12 months of age should be retained.

For children and adolescents aged 10-17 years, there is limited evidence from two studies showing that vitamin D intakes at doses up to 50 µg/day do not lead to hypercalcaemia. While there are no

studies at higher intakes, it was considered that there is no reason to believe that adolescents in the phase of rapid bone formation and growth have a lower tolerance for vitamin D compared to adults, and a UL of 100 µg/day for adolescents aged 11-17 years was proposed.

For children aged 1-10 years, no new data from intervention studies have emerged since the previous risk assessment. It was considered that there is no reason to believe that children aged 1-10 years in the phase of rapid bone formation and growth have a lower tolerance for vitamin D compared to adults, and, by taking into account their smaller body size, a UL for vitamin D of 50 µg/day was proposed.

Data from European populations indicate that vitamin D intakes from all sources in high consumers are below the UL for all population subgroups (i.e., about 25 %, 75 %, 30 % and 8 % of the UL for adults, infants, children and adolescents, respectively).

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Vitamin D has been assessed in the past by the Scientific Committee on Food. In the Opinion on the Tolerable Upper Intake Level (UL) of vitamin D of 4 December 2002 the Committee set the following UL values for vitamin D:

- 50 µg vitamin D/day for adults;
- 25 µg vitamin D/day for infants 0-2 years of age;
- 25 µg vitamin D/day for children from 3-10 years of age;
- 50 µg vitamin D/day for adolescents 11-17 years of age.

On 30 November 2010, the American Institute of Medicine (IoM) published a report on “*Dietary Reference Intakes for Calcium and Vitamin D*” (IoM, 2010). In this report, the IoM proposes new reference values and UL values for vitamin D which, as stated in the report “*are based on much more information and higher-quality study results than were previously available*”.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to:

- re-evaluate the safety in use of vitamin D,
- if necessary, provide revised tolerable upper intake levels, that are unlikely to pose a risk of adverse health effects, for vitamin D for all relevant population groups.

ASSESSMENT

1. Introduction

The principal physiological function of vitamin D in all vertebrates including humans is to maintain serum calcium and phosphorus concentrations in a range which supports cellular processes, neuromuscular function, and bone ossification.

It has become increasingly apparent that vitamin D also has other important functions in tissues not primarily related to mineral metabolism (Bouillon et al., 2008; Holick, 2006). Examples are its role in modulating the renal production of renin and its role in insulin secretion. The active metabolite, 1,25(OH)₂D, regulates the transcription of a large number of genes through binding to a transcription factor, the vitamin D receptor.

In 2003, the Scientific Committee on Food (SCF, 2003) established a Tolerable Upper Intake Level (UL) of vitamin D for adults, including pregnant and lactating women, of 50 µg/day. This UL was based on the increased risk of hypercalcaemia observed after intakes of around 100 µg vitamin D/day in the highest dose group in one (Narang et al., 1984) of three studies. An uncertainty factor of 2 was applied to account for inter-individual variation. For infants and young children aged 0-24 months the UL was set at 25 µg/day based on the absence of hypercalcaemia attributable to intervention with vitamin D in two studies in which breast-fed or formula-fed infants received 25 µg vitamin D/day (plus the amount ingested via fortified infant formula) for some months. The UL for children aged 3-10 years was set at 25 µg/day and for adolescents aged 11-17 years at 50 µg/day, though data on supplementation with vitamin D doses ≥ 20 µg/day were lacking.

The UL for vitamin D for adults established by the SCF (2003) was 50 µg/day, the same as that from the US Institute of Medicine (IoM, 1997). It was derived from a no observed adverse effect level (NOAEL) of 60 µg/day, by applying an uncertainty factor of 1.2 to account for the small sample size and short duration of the single study (Narang et al., 1984) on which the NOAEL was based. The same UL of 50 µg/day was set for pregnant and lactating women and for children beyond one year of age. For infants, a UL of 25 µg/day was set based on normal growth in formula-fed infants ingesting 34.5-54.3 µg vitamin D/day, by applying an uncertainty factor of 1.8 to the mean of the lower and upper dose range (44.4 µg) to account for the insensitivity of the end point and the small sample size of the study.

In 2011, the IoM published its re-assessment of the UL for vitamin D and considered an intake of 250 µg vitamin D/day as a NOAEL, but also used information on 25(OH)D concentrations achieved during considerable sun exposure as well as evidence from observational studies on chronic disease outcomes suggesting an increase in risk associated with 25(OH)D concentrations above approximately 125 to 150 nmol/L. Based on one dose-response study, vitamin D intakes of 125 µg/day were judged as not increasing 25(OH)D concentration beyond 150 nmol/L. An uncertainty factor of 1.2 was applied to take into account various uncertainties and the reliance on a single study. The UL for adults, including pregnant and lactating women, was set at 100 µg/day. The same UL was set for children and adolescents aged 9-18 years, while the value was scaled down for young children and those aged 4-8 years. For infants aged 0-6 months, a UL of 25 µg/day was set based on normal growth in infants receiving a mean of 44.4 µg vitamin D/day, applying an uncertainty factor of 2 to ensure absence of toxicity also in small infants, and then rounding. In infants aged 6-12 months with a greater body size, the UL was set at 38 µg/day (IoM, 2010).

This opinion relates to the evaluation of the safety in use of vitamin D forms authorised for addition to foods⁴ or food supplements⁵, i.e. cholecalciferol (vitamin D₃) and ergocalciferol (vitamin D₂). The two forms only differ by their side chains on the sterol skeleton (Holick, 2006). The term vitamin D without a subscript relates to either or both vitamin D₂ or vitamin D₃ and its metabolites. Only data on oral intake of vitamin D will be considered for this opinion.

2. Dietary intakes

Few foods naturally contain vitamin D. Some higher fungi such as mushrooms are a natural source of vitamin D₂. Animal foods such as fatty fish, liver, fish liver oils and egg yolks contain vitamin D₃. Further sources of vitamin D are fortified foods (most often milk, margarine and/or butter, and breakfast cereals) and dietary supplements.

Mean intakes of vitamin D in European countries vary according to sex, age, and supplementation habits (Appendices A and B). There is a large diversity in the methodology used to assess the individual intakes of children, adolescents and adults. These differences in dietary assessment methods make direct comparisons difficult. Data from Poland based on a single 24-h recall have been listed in Appendices A and B for completeness but have not been considered in the text. Age classifications may not be uniform and comparability is also hindered by differences in food composition tables used for the conversion of food consumption data to nutrient intake data (Deharveng et al., 1999). Although these differences have an impact on the accuracy of between-country comparisons, the data presented give a rough overview of average vitamin D intakes and intakes in high consumers in a number of European countries.

2.1. Adults

Mean intakes of vitamin D from foods only varied from 1.1 µg/day (Spain, women, 18-64 years) to 8.2 µg/day (Finland, men, 25-74 years). The 95th percentiles varied between 2.4 µg/day (Spain, women, 18-64 years) and 16.0 µg/day (Finland, men, 25-74 years).

When foods and supplements were considered together, mean intakes of vitamin D varied from 3.1 µg/day (Ireland, women, 18-35 years) to 23.5 µg/day (Norway, men in the fourth quartile of n-3 long-chain polyunsaturated fatty acid intake, 16-79 years). Intakes at the 95th percentile varied between 6.3 µg/day (The Netherlands, women, 19-30 years) and 24.2 µg/day (Ireland, ≥65 years).

The Panel notes that the range of vitamin D intakes reported from 14 European countries is considerable. In high consumers (95th percentile), intakes from foods are up to 16 µg/day, and about 1.5-fold this value in those that consume supplements in addition to foods.

2.2. Infants (≤1 year)

For infants, mean intakes from foods and supplements were available from Finland and The Netherlands, and varied between 8.9 µg/day (The Netherlands, 1 year) and 12.5 µg/day (The Netherlands, 0.75 years). The 90th percentiles were between 14.8 and 19.3 µg/day in Dutch infants aged 1 and 0.75 years, respectively. The high percentiles available for Finland (P75) were within this range.

⁴ Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. OJ L 404, 30.12.2006, p. 26-38.

⁵ Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. OJ L 183, 12.07.2002, p. 51-57.

2.3. Children (approximately 1-14 years)

In younger children, mean intakes from foods varied from 1.7 µg/day (Denmark, boys, 1-3 years) to 5.6 µg/day (Greece, 1-5 years). The values for high percentiles were between 2.4 µg/day (Denmark, P95, boys, 1-3 years) and 11.9 µg/day (Greece, P90, 1-5 years). Mean vitamin D intakes from foods and supplements varied from 2.3 µg/day (UK, 1.5-3 years) to 9.0 µg/day (Finland, girls, 2 years). The 90th percentile in Dutch children aged 1.5 years was 8.1 µg/day. The high percentiles available for Finland (P75) were even higher, i.e. 9.5 and 12.6 µg/day in boys and in girls, aged 2 or 3 years.

In older children, mean or median intakes from foods only varied from 1.4 µg/day (mean, Spain, 4-10 years; Ireland, boys, 5-12 years) to 2.7 µg/day (The Netherlands, median, boys, 9-13 years). Intakes at the 95th percentile were between 2.9 µg/day (Spain, 4-10 years, including fortified food) and 5.9 µg/day (Denmark, 4-14 years). Average intakes from foods and supplements varied from 1.8 µg/day (mean, Germany, 6-11 years; Spain, 4-10 years) to 6.6 µg/day (Sweden, mean, 4 years). Intakes at the 95th percentile were between 3.0 µg/day (Spain, 4-10 years) and 15.4 µg/day (Sweden, 4 years).

2.4. Adolescents

In adolescents, mean intakes from foods varied from 1.6 µg/day (Spain, 11-17 years) to 4.0 µg/day (Belgium, boys 13-18 years). Intakes at the 95th percentile were between 3.0 µg/day (Spain, 11-17 years) and 7.7 µg/day (Italy, boys, 10-<18 years, including fortified food). Mean or median intakes from foods and supplements and for the 95th percentile of consumption are within these ranges.

The Panel notes that in infants, children and adolescents from 11 European countries, the highest intakes from foods and supplements are observed in infants (up to about 19 µg/day at the 90th percentile), while the intake in high consumers is lower in children (up to about 15 µg/day at the 95th percentile) and even lower in adolescents (up to about 8 µg/day at the 95th percentile).

3. Hazard identification

3.1. Vitamin D physiology

Vitamin D derives from diet but can also be synthesised in the skin from 7-dehydrocholesterol under the influence of UV-B radiation (290–315 nm wavelengths), leading to the formation of previtamin D₃. Previtamin D₃ thermally isomerises to vitamin D₃ immediately after formation. Sunlight itself regulates the total production of vitamin D₃ in the skin, as both previtamin D₃ and vitamin D₃ present in the skin are photodegraded to biologically inert isomers following prolonged UV-B exposure. Dietary intake of vitamin D increases 25(OH)D concentrations without an equivalent regulatory mechanism, with a linear relationship between vitamin D intakes and serum 25(OH)D concentrations well into the high dose range (Holick, 2006). The 24-hydroxylase catabolises 25(OH)D to 24,25(OH)₂D to prevent its eventual activation to 1,25(OH)₂D (Jones et al., 2012). Following vitamin D supplementation, 24-hydroxylase is upregulated, though this adaptation occurs with a lag of several weeks (Wagner et al., 2011).

Both 25- and 1α-hydroxylation of vitamin D are needed to form the active metabolite 1,25(OH)₂D. At least four enzymes, all microsomal cytochrome P₄₅₀ (CYP) isoforms (CYP2DII, CYP2D25, CYP3A4, and CYP2R1), can accomplish the 25-hydroxylation of vitamin D in human hepatocytes. Little feedback is assumed for these 25-hydroxylases, and serum 25(OH)D concentration generally reflects vitamin D status. Serum 1,25(OH)₂D, the active metabolite, is synthesised in the kidney, where the activity of the enzyme 25(OH)D-1α-hydroxylase (CYP27B1) is regulated by calcium and phosphate, as well as by their regulating hormones (calcium, parathyroid hormone, calcitonin, growth

hormone, and insulin-like growth factor I being positive regulators; phosphate, fibroblast growth factor 23, and 1,25(OH)₂D itself being negative regulators). The active metabolite exerts its action through binding to the vitamin D receptor and activating a nuclear transcription factor (Bouillon et al., 2008).

The principal function of the active metabolite (1,25(OH)₂D) is to maintain intracellular and extracellular calcium concentrations within a physiologically acceptable range. This regulation is accomplished by enhancing the efficiency of the small intestine in absorbing dietary calcium and phosphorus, and by mobilising calcium and phosphorus from the bone.

3.2. Biomarkers of vitamin D intake

The concentration of 25(OH)D in plasma or serum can only be used as a biomarker of vitamin D intake in people with low exposure to sunshine. After initiation of vitamin D supplementation, a new steady state is reached after six to eight weeks in adults (Seamans and Cashman, 2009). It has been suggested that whereas vitamin D₂ and vitamin D₃ may equally increase 25(OH)D concentrations when supplemented daily, vitamin D₃ may raise 25(OH)D concentrations more than vitamin D₂ if single or infrequent bolus doses are administered (Tripkovic et al., 2012).

3.3. Biomarkers of vitamin D status and activity

There is consensus that serum 25(OH)D concentration is a good marker of vitamin D status (Seamans and Cashman, 2009). The 25(OH)D denotes both D₂ and D₃ metabolites. Plasma 25-hydroxyergocalciferol (25(OH)D₂) is of exogenous origin only, while 25-hydroxycholecalciferol (25(OH)D₃) may arise from either dietary intake or formation in the skin. Plasma concentration of 1,25(OH)₂D (particularly free 1,25(OH)₂D) is a measure of vitamin D hormone activity, but because of tight homeostatic regulation, 1,25(OH)₂D does not reflect vitamin D nutritional status.

Owing to its slow turnover in the body (half-life of about two months (Jones, 2008)), vitamin D is often administered weekly in equivalent doses instead of daily. Depending on the dose and the duration of supplementation, resulting 25(OH)D concentrations may be comparable (Ish-Shalom et al., 2008) or somewhat lower (Chel et al., 2008) with weekly compared to daily supplementation, respectively.

The main determinants, besides intake, of vitamin D status are skin pigmentation and sun exposure. Concentrations of 25(OH)D vary according to season, with the lowest concentrations occurring at the end of winter and the highest concentrations in summer (Hintzpeter et al., 2008), generally reflecting the amount of endogenous synthesis following UV-B radiation. Latitude of residence and time of day also determine the amount of UV-B photons penetrating the stratospheric layer and resulting in cutaneous synthesis of previtamin D₃ in exposed skin (Holick, 2006). Below a latitude of approximately 35° North, UV-B radiation is sufficient for vitamin D₃ synthesis all year round. At higher latitudes, there is no cutaneous vitamin D₃ synthesis during the winter months. For example, in Rome, Italy (latitude 41.9° North), cutaneous vitamin D₃ synthesis is not possible from November through February. Ten degrees further north in Berlin, Germany (latitude 52.5° North) or Amsterdam, the Netherlands (latitude 52.4° North), vitamin D₃ synthesis ceases between October and April (Tsiaras and Weinstock, 2011). Vitamin D intoxication by UV-B radiation alone has not been reported (Webb et al., 1989). Mean (range) 25(OH)D concentrations under sun-rich living conditions were 133 (27-277) nmol/L in 18 farmers in Puerto Rico (Haddock et al., 1982), 161 (132-197) nmol/L in eight lifeguards in St. Louis (USA) (Haddad and Chyu, 1971), and 133±84 nmol/L in 44 Israeli lifeguards (Better et al., 1980). Following extended exposure to sunlight during summer, median (interquartile range) 25(OH)D concentrations in late summer were 122 (95-154) nmol/L in 26 young men for whom sun exposure was the principal source of vitamin D, with the highest concentration

being 211 nmol/L. The median (interquartile range) seasonal difference in 25(OH)D concentration between late summer and late winter was 49 (29-67) nmol/L (Barger-Lux and Heaney, 2002).

Further determinants of vitamin D status are age and body mass, with lower 25(OH)D concentrations observed in advanced age (Hintzpeter et al., 2008; Holick, 2006) and in obesity (Hintzpeter et al., 2008; Kauppi et al., 2009; Macdonald et al., 2008; Snijder et al., 2005).

The amount of vitamin D in human milk is modestly correlated with maternal vitamin D intakes up to about 18 µg/day, with evidence for a lower response in African-American compared to white women (Specker et al., 1985). Few data are available to estimate precisely the increase in human milk vitamin D concentration in response to supplemental vitamin D (Ala-Houhala et al., 1986; Hollis and Wagner, 2004; Specker et al., 1985). Infants of mothers supplemented with 50 or 100 µg vitamin D/day during months 1-4 of lactation only differed slightly in serum 25(OH)D concentration (Hollis and Wagner, 2004), pointing to a limitation of vitamin D transfer into human milk.

3.4. Mechanisms of toxicity

Following ingestion of large doses of vitamin D, the concentration of 25(OH)D in serum increases, while that of the active metabolite 1,25(OH)₂D is unchanged (Jones, 2008) or even reduced (IoM, 2010). However, at high concentrations of 25(OH)D and other vitamin D metabolites (such as 24,25(OH)₂D₃, 25,26(OH)₂D₃, and 25(OH)D₃-26,23-lactone) the binding capacity of the vitamin D binding protein may be exceeded, leading to the release of unbound 25(OH)D and 1,25(OH)₂D. It has been hypothesised that these free forms enter target cells and directly stimulate gene transcription (Bouillon et al., 2008). However, severe hypercalcaemia and weight loss after administration of vitamin D have been observed in a mouse model which is unable to synthesise 1,25(OH)₂D, suggesting that 25(OH)D rather than 1,25(OH)₂D may be mediating toxicity (DeLuca et al., 2011).

Very high serum 25(OH)D concentrations (which may displace 1,25(OH)₂D from vitamin D-binding protein) may lead to hypercalcaemia (Holick, 2006; Pettifor et al., 1995; Vieth, 1990), which is defined by serum calcium concentrations >2.75 mmol/L (11 mg/dL). Values used for the diagnosis of hypercalcaemia may change across laboratories and will be defined in this opinion according to the cut-off selected by the authors in each individual study. Clinical symptoms associated with hypercalcaemia are fatigue, muscular weakness, anorexia, nausea, vomiting, constipation, tachycardic arrhythmia, soft tissue calcification, failure to thrive, and weight loss. Hypercalcaemia may also lead to hypercalciuria, which is defined by a calcium excretion >0.3 mg/mg creatinine in 24-hour urine of adults, or as a calcium excretion >250 mg/day in women and >275-300 mg/day in men. Consequences of sustained hypercalcaemia are nephrolithiasis (kidney stones), nephrocalcinosis, and a decrease in kidney function (see also the Scientific Opinion on the Tolerable Upper Intake Level of calcium (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2012).

3.5. Adverse effects of excess vitamin D intake

3.5.1. Vitamin D intake and hypercalcaemia in adults

In 2003, the SCF derived a UL of 50 µg vitamin D/day for adults (SCF, 2003). In this section, new evidence which has become available since 2003 will be described in conjunction with the evidence used to derive the previous NOAEL of 100 µg vitamin D/day for adults. Intervention studies in which vitamin D was administered weekly or more frequently in doses equivalent to intakes between 60 and 1,269 µg/day, and which reported on serum calcium concentrations and/or the occurrence of hypercalcaemia, have been considered (see also Appendix C).

Studies with vitamin D doses up to 275 µg/day

A number of intervention studies in humans have reported on the effects of vitamin D supplementation at doses up to 275 µg/day on calcaemia and calciuria (Appendix C). Several studies monitored serum calcium concentrations at several time points throughout the study and addressed possible adverse effects as secondary outcomes. The majority of the studies were randomised controlled trials (RCTs) in which vitamin D supplementation was compared to a placebo (Aloia et al., 2008; Gallagher et al., 2012; Heaney et al., 2003; Jorde et al., 2010; Sneve et al., 2008; Zittermann et al., 2009) or to a lower dose of vitamin D (Grimnes et al., 2012; Narang et al., 1984; Vieth et al., 2001). One was a dose-response study using four different doses of vitamin D in the range of 0-275 µg/day (Heaney et al., 2003). One controlled study was not randomised (Berlin et al., 1986; Berlin and Björkhem, 1987), one was a two-arm intervention with no control group (Tjellesen et al., 1986), and one was a one-arm intervention with no control group (Mocanu et al., 2009). Considering only the highest dose in studies using multiple doses, the equivalent daily vitamin D doses ranged from 83 to 275 µg, and the duration of the supplementation from seven weeks to 12 months. In addition to vitamin D, subjects received supplemental calcium in five studies: four studies used doses ranging from 320 to 1,000 mg/day (Grimnes et al., 2012; Jorde et al., 2010; Mocanu et al., 2009; Tjellesen et al., 1986), while supplemental calcium intake was adjusted individually to achieve a total calcium intake of 1,200-1,400 mg/day in the study by Gallagher et al. (2012). The shorter-term studies were generally performed in seasons of low sun exposure. Study populations were not generally vitamin D-deficient, and two studies (Grimnes et al., 2012; Heaney et al., 2003) were conducted in subjects with a high vitamin D status at baseline. Study populations included whites, African Americans, young men, pre- and postmenopausal women, elderly nursing home residents, and overweight and obese adults.

The study by Narang et al. (1984) reported mean serum calcium concentrations to be slightly above the normal range in the few subjects who received the highest vitamin D dose (95 µg/day). The Panel notes that these results are not in line with the findings of studies using similar or (much) higher doses of vitamin D. The Panel also notes that this study did not include a true (non-vitamin D) control group, and that no information on serum 25(OH)D concentration, season of the trial, background vitamin D intake and persistence of elevated serum calcium concentration was provided.

In the dose-response study by Heaney et al. (2003), in which men received either 0, 20.9, 137.5 or 275 µg vitamin D₃/day for 20 weeks, mean serum calcium concentrations measured at five time points during the study in the two groups receiving the highest doses of vitamin D did not change significantly from baseline and remained below the upper limit of normal (<2.6 mmol/L) for all of the 31 subjects in these groups.

None of the remaining studies reported persisting or occasional hypercalcaemia and/or hypercalciuria which could be attributed to vitamin D supplementation. The Panel notes that several studies used doses of vitamin D >95 µg/day.

The Panel concludes that vitamin D at doses up to 275 µg/day do not lead to persisting hypercalcaemia or hypercalciuria in adults.

Studies with vitamin D doses >275 µg/day

In an open-label study, Barger-Lux et al. (1998) administered 35, 234 or 1,269 µg vitamin D₃/day for eight weeks to 38 men (n=14 in the highest dose group). The authors stated that post-treatment testing indicated absence of hypercalcaemia in vitamin D₃-supplemented subjects, but no further information, including a definition of hypercalcaemia, was given. The Panel notes that the serum concentrations of 25(OH)D reported in this study for the highest dose group (about 710 nmol/L) were far above those observed following considerable sun exposure (serum 25(OH)D concentration between around 120 and 160 nmol/L, see Section 3.3).

Hypercalcaemia owing to high intakes of vitamin D in dietary supplements (e.g. Araki et al. (2011); Lowe et al. (2011)) or in milk (Blank et al., 1995; Jacobus et al., 1992) has been reported. Doses of vitamin D and duration of supplementation cannot be estimated precisely from these case reports.

In some studies, higher doses of vitamin D (twice weekly administration equivalent to 321 µg vitamin D₂/day, 450 µg vitamin D₂/day) were part of the treatment regimen for various diseases, and its use for weeks to years was not associated with increased serum calcium concentrations or hypercalcaemic episodes (Hasling et al., 1987; Rickers et al., 1982). However, these findings are difficult to interpret because of the concomitant administration of substances that may have confounded the outcome (e.g. prednisone and/or sodium fluoride), and because of the use in small groups of patients with various diseases. For the same reasons, evidence from case reports of vitamin D intoxication after administration of vitamin D for the treatment of osteoporosis, osteomalacia, hypoparathyroidism or other diseases (Davies and Adams, 1978; Rizzoli et al., 1994; Schwartzman and Franck, 1987; Selby et al., 1995) (see Appendix C) cannot be used for the establishment of a UL for healthy adults.

The Panel notes that the data available from these studies and case reports on vitamin D at intakes >275 µg/day are not suitable for establishing a UL for long-term intakes.

3.5.2. Serum 25(OH)D concentration and hypercalcaemia in adults

Following supplementation with up to 275 µg vitamin D₃/day for 20 weeks, Heaney et al. (2003) observed a mean 25(OH)D concentration of about 220 nmol/L without concomitant hypercalcaemia.

Vieth (1999) reviewed case reports of vitamin D toxicity and concluded that hypercalcaemia owing to vitamin D intoxication *per se* is always accompanied by serum 25(OH)D concentrations >220 nmol/L. Other reviews suggested that hypercalcaemia only resulted at 25(OH)D concentrations consistently exceeding 375-500 nmol/L (Jones, 2008), or ≥700 nmol/L in normal adults (Hathcock et al., 2007). In four cases of vitamin D intoxication in osteoporotic women, 25(OH)D concentrations between 339 and 804 nmol/L were observed during the course of diagnosis and treatment (Schwartzman and Franck, 1987). Araki et al. (2011) reported hypercalcaemia in two cases of vitamin D intoxication following ingestion of erroneously manufactured and labelled vitamin D supplements; both patients became normocalcaemic and asymptomatic once 25(OH)D concentrations decreased below 998 nmol/L. In 19 case reports on hypercalcaemia, serum 25(OH)D concentrations of 533-1,692 nmol/L were reported after a daily vitamin D intake between 1,250 µg and 7,500 µg for three weeks to several years (Davies and Adams, 1978; Rizzoli et al., 1994; Selby et al., 1995); however, one woman who presented with hypercalcaemia after receiving the equivalent of 2,143 µg vitamin D₃/day for 96 weeks had a plasma 25(OH)D concentration of only 221 nmol/L (Rizzoli et al., 1994).

The Panel concludes that 25(OH)D concentrations associated with hypercalcaemia vary over a wide range, and that the 25(OH)D concentration in serum or plasma cannot be considered a suitable predictor of hypercalcaemia.

3.5.3. Vitamin D intake or status and long-term health outcomes in adults

A wealth of observational and intervention studies has been performed in recent years on the association between vitamin D intake or status and various chronic diseases. The studies generally adjusted for season. Most of the observational studies (Anderson et al., 2010; Cawthon et al., 2010; Eaton et al., 2011; Ford et al., 2011; Ginde et al., 2009; Hutchinson et al., 2010; Jia et al., 2007; Semba et al., 2009; Semba et al., 2010; Virtanen et al., 2011; Visser et al., 2006) aimed at evaluating the role of vitamin D insufficiency as a risk factor, but some also took into account potential adverse

effects of high serum 25(OH)D concentrations or high vitamin D intake and allowed for non-linear associations when analysing relationships.

Of these, some observational studies found a U-shaped or reverse J-shaped association between 25(OH)D concentrations and all-cause mortality, with a significant increase in risk in elderly Swedish men with concentrations >98 nmol/L (but not >93 nmol/L) (Michaelsson et al., 2010) and in US females (but not in men or both sexes combined) with concentrations >124.8 nmol/L (Melamed et al., 2008). In some studies, the higher risk associated with the highest 25(OH)D concentrations did not hold for longer times of follow-up (Johansson et al., 2011) or did not consider important possible confounders such as smoking, body mass index (BMI) and health status (Durup et al., 2012). Evidence from a meta-analysis of randomised primary and secondary prevention trials which provided data for mortality analyses showed that a dose ≥ 20 μ g vitamin D₃/day (n=21 studies) or ≥ 20 μ g vitamin D₂/day (n=12 studies) administered over a median of two years did not affect all-cause mortality (Bjelakovic et al., 2011). These results are in line with findings of another meta-analysis that did not observe an effect of vitamin D doses ≥ 20 μ g/day on mortality as observed in 20 randomised trials (Elamin et al., 2011).

Some studies performed subgroup analyses according to the cause of death. A significant increase in total cancer mortality was observed in Swedish elderly men with baseline serum 25(OH)D concentrations >98 nmol/L (but not >93 nmol/L) (Michaelsson et al., 2010), and in US men (but not in women) with 25(OH)D concentrations in the highest two categories (80–<100 nmol/L and ≥ 100 nmol/L) compared to men with 25(OH)D concentrations <37.5 nmol/L, though the overall trend was not significant (Freedman et al., 2010). In other cohort studies (Cawthon et al., 2010; Eaton et al., 2011; Hutchinson et al., 2010; Melamed et al., 2008), either no association or an inverse association between 25(OH)D concentration and risk for mortality from cancer was reported. A meta-analysis of observational studies published up to July 2011 showed no association between 25(OH)D concentration and breast cancer (five studies) or prostate cancer (11 studies), and an inverse association with colorectal cancer (nine studies) (Chung et al., 2011). In RCTs using vitamin D doses between 10 and 27.5 μ g/day and lasting four to seven years in which cancer of the breast or colon were secondary outcomes, there was no evidence of an increased cancer risk in subjects receiving vitamin D (Chlebowski et al., 2008; Lappe et al., 2007; Wactawski-Wende et al., 2006). In a nested case-control study with participants from eight prospective cohorts, there was a significantly increased risk for pancreatic adenocarcinomas for subjects with 25(OH)D concentrations ≥ 100 nmol/L, but the risk pattern was rather peculiar with a flat trend line (risk close to 1 in all other categories of 25(OH)D concentration) followed by a steep inflection for the subjects in the highest category (Stolzenberg-Solomon et al., 2010). In two US cohorts for which only intake data were available, the association between vitamin D intake and pancreatic cancer was inverse (Skinner et al., 2006).

Several studies also addressed the relationship between 25(OH)D concentration and cardiovascular disease, but no evidence of an increased risk for fatal and non-fatal cardiovascular events associated with high concentrations of 25(OH)D was found in observational studies (Cawthon et al., 2010; Eaton et al., 2011; Fiscella and Franks, 2010; Grandi et al., 2010; Hutchinson et al., 2010; Jassal et al., 2010; Michaelsson et al., 2010; Virtanen et al., 2011).

On other health outcomes, an observational study reported a significantly increased risk for self-reported fractures in black women with 25(OH)D concentrations ≥ 49.9 nmol/L (compared to <49.9 nmol/L), whereas the association was inverse for white women (Cauley et al., 2011). In women receiving 1 g calcium plus 10 μ g vitamin D daily for a mean of seven years, a higher incidence of self-reported urinary tract stones was reported compared to those receiving placebo (Wallace et al., 2011). Plasma or serum 25(OH)D concentrations were not measured in this study. The Panel notes that the low dose of vitamin D used, and the nature of the combined nutrient supplementation, do not allow the attribution of the reported adverse effect to vitamin D intake *per se*.

The Panel notes that no studies reported an association between vitamin D intake and increased risk for adverse long-term health outcomes, and that studies reporting on an association between 25(OH)D concentration and all-cause mortality or cancer are inconsistent. The Panel also notes that when 25(OH)D concentrations were associated with an increased risk for adverse long-term health outcomes in some studies, there was a wide variation in 25(OH)D concentrations associated with the adverse effect. The Panel considers that 25(OH)D concentrations cannot be used to characterise the risk for adverse long-term health outcomes.

3.5.4. Adverse effects of vitamin D intake in pregnant and lactating women

De-Regil et al. (2012) systematically searched the literature for RCTs which evaluated the effect of supplementation with vitamin D alone or in combination with calcium on women during pregnancy. Six RCTs published up to October 2011 were included for meta-analysis. The dose of vitamin D used in routine daily supplementation ranged from 20-30 µg. The studies reported on pre-eclampsia, nephritic syndrome, and stillbirths or neonatal deaths, and there was no difference in risk between pregnant women receiving vitamin D and those receiving placebo.

Hollis et al. (2011) randomly assigned pregnant women to receive either 10 µg, 50 µg or 100 µg vitamin D₃/day from 12-16 weeks of gestation until delivery. The primary outcome was change in maternal serum 25(OH)D concentrations, but the study also addressed the safety of vitamin D supplementation and pregnancy outcomes. Of the 502 women randomised, only 350 were followed through delivery, and no attempt was made to assess pregnancy outcomes in those who discontinued from the study for reasons other than miscarriage. The number of, and gestational age at, pregnancy losses, and the serum 25(OH)D concentrations in those affected, did not differ between the groups (n=8, 5, 10 in the groups receiving 10 µg, 50 µg or 100 µg vitamin D₃/day, respectively). Mode of delivery, pregnancy duration, birth weight and neonatal level of care required after birth also did not differ. No information on the nature of adverse events was given in the study, but the authors stated that no adverse event was attributed to vitamin D supplementation or serum 25(OH)D concentrations. Throughout the trial, the groups did not differ with respect to serum calcium and urinary calcium-to-creatinine ratio. It was decided *a priori* to discontinue supplementation in women exceeding a 25(OH)D concentration of 225 nmol/L as a safety measure. Three women (one in the 100 µg vitamin D₃/day group) attained this threshold without accompanying hypercalcaemia or hypercalciuria.

In another study, lactating women (n=18) randomly received either 40 µg vitamin D₂+10 µg vitamin D₃/day or 90 µg vitamin D₂+10 µg vitamin D₃/day from month 1 through 4 of lactation during which time they were asked to limit sun exposure (Hollis and Wagner, 2004). Serum calcium concentrations remained within the normal range and hypercalciuria did not occur. Serum 25(OH)D concentrations increased from 69±8 to 90±6 nmol/L in the group receiving 40 µg vitamin D₂+10 µg vitamin D₃/day and from 82±6 to 111±10 nmol/L in the group receiving 90 µg vitamin D₂+10 µg vitamin D₃/day. In the infants, concurrent increases in serum 25(OH)D concentration were observed resulting from an increase in vitamin D intake via human milk. In infants whose mothers received the lower vitamin D dose, total circulating 25(OH)D concentrations increased from 20±3 to 69±10 nmol/L, whereas concentrations increased from 33±8 to 77±12 nmol/L in infants of mothers receiving the higher vitamin D dose.

In a nested case-control study, a U-shaped association was observed in white (n=77 cases, 196 controls) but not in black (n=34 cases, 105 controls) nulliparous women between 25(OH)D concentrations in the first half of pregnancy (<22 weeks) and birth of a small-for-gestational age (SGA) infant (Bodnar et al., 2010). In white women, the odds ratio (OR) was 2.1 (95 % CI 1.2-3.8) for a serum 25(OH)D concentration >75 nmol/L (reference category 37.5-75 nmol/L). The Panel notes that it is unclear whether a one-time measurement of vitamin D status in early pregnancy reflects vitamin D status throughout pregnancy, that no intake data are available linking vitamin D

intake to an increased risk for an SGA infant, and that only a limited number of possible dietary and lifestyle confounders were taken into account in the analyses. Thus, the Panel considers that no conclusions can be drawn from this study in relation to the effects of vitamin D intake on pregnancy outcomes.

The Panel considers that evidence from one intervention trial in pregnant women receiving vitamin D after the period of early organogenesis and from another small trial in lactating women, both using doses of vitamin D₂ or D₃ up to 100 µg/day for several weeks to months, did not report adverse events for either the mothers or their offspring.

3.5.5. Adverse effects of vitamin D intake in infants

In infants, hypercalcaemia has been associated with single large dose therapies of vitamin D (also known as stoss therapy). The potential toxicity associated with stoss therapy is underscored by a report showing hypercalcaemia in a young child who received the equivalent of four daily stoss therapy doses of 15 mg vitamin D each (Barrueto et al., 2005). The Panel notes that no information on effects of chronic daily intake relevant for the establishment of a UL can be derived from such case reports.

A number of studies with lower daily doses of vitamin D are available.

Jeans and Stearns (1938) found retarded linear growth in nine infants up to one year of age who received about 45-112.5 µg vitamin D/day in comparison with standard growth curves of infants receiving daily vitamin D at doses of 8.5 µg or less for a minimum of six months. The infants were given either cod liver oil, a cod liver oil concentrate emulsified in cream, or viosterol (vitamin D₂) in oil. The infants supplemented with high doses of vitamin D showed retarded linear growth, and increased rates of growth were seen when the dose of vitamin D was reduced to 10-15 µg/day. In another study, Fomon et al. (1966) compared 13 formula-fed infants who ingested 34.5-54.3 µg vitamin D/day (median intake 45 µg/day) with 11 infants who ingested 8.8-13.8 µg/day (median intake 11 µg/day). The infants were enrolled before the age of nine days and were followed-up at ages 28, 56, 84, 112, 140 and 168 days. A group of 26 breast-fed infants was also followed. No differences in linear growth and in serum calcium concentrations were found between groups in this small study.

Data from a Finnish population-based birth cohort was used to assess retrospectively the association between infantile vitamin D supplementation and body height at various time points until adulthood (Hyppönen et al., 2011). No association of vitamin D dose (<50 µg/day, n=66; 50 µg/day according to the Finnish recommendations at that time, n=8,100; and >50 µg/day, n=407) in regularly supplemented infants with body length or height at one year (measured), at 14 years (self-reported) and in adulthood (self-reported and measured) was reported. No difference in height was observed between groups classified according to frequency of supplementation (none, irregular, or regular), but again the groups were highly unequally sized.

In a study from Finland, Ala-Houhala (1985) supplemented breast-fed infants with 0, 10 or 25 µg vitamin D₂/day for 20 weeks (14-17 infants per group). Mothers of infants not taking vitamin D received 25 µg/day. Two studies were conducted, one starting in January and the other starting in July. Mean serum calcium concentrations in infants did not appear to increase throughout the study in either group.

Vervel et al. (1997) studied healthy neonates born from April to July of mothers supplemented (n=22) or not supplemented (n=48) with vitamin D during pregnancy. The infants were given supplemental vitamin D₂ (either 12.5 or 25 µg/day). In addition, they were fed infant formulae chosen by the mothers and thus varying slightly in vitamin D content (10.7±1.2 µg/L). All 70 infants were followed until the age of one month, and 52 infants were followed until three months of age. Mean serum

calcium concentrations did not differ between groups at one and three months of age. Serum calcium concentrations at three months ranged from 2.42 to 2.80 mmol/L in infants who received 12.5 µg vitamin D/day in addition to fortified infant formula, and from 2.46 to 2.79 mmol/L in those supplemented with 25 µg vitamin D/day; the percentage of infants presenting with serum calcium concentrations >2.6 mmol/L was lower in the higher vitamin D group compared to the lower vitamin D group.

In a randomised study, infants and toddlers with hypovitaminosis D (25(OH)D concentration <50 nmol/L) aged between 9 and 23 months were treated for six weeks with either 50 µg vitamin D₂ daily (n=12), 1,250 µg vitamin D₂ weekly (n=14), or 50 µg vitamin D₃ daily (n=14), and each group also received 50 mg calcium/kg body weight per day (Gordon et al., 2008). Small and similar changes in mean serum calcium concentrations in the three treatment groups (-3 % for vitamin D₂ daily, +3 % for vitamin D₂ weekly, +1 % for vitamin D₃ daily) were reported, as well as a higher overall incidence of mild hypercalcaemia at baseline compared to after treatment, but no definition was given as to the normal range of calcium concentrations in serum. All subjects with mild hypercalcaemia were reported to be asymptomatic. The Panel notes that this was a short study using high vitamin D doses for treatment of deficiency, and considers that limited conclusions can be drawn from this study for the purpose of this risk assessment.

The Panel notes that there is historical evidence on retarded growth from one study in infants who received various regimens of vitamin D exceeding 45 µg/day up to one year of age, although another small study using doses up to 54 µg vitamin D/day until about five months of age did not show such an effect. More recent intervention studies using doses up to 25 µg vitamin D/day (plus the amount ingested via fortified infant formula) for up to five months after birth did not indicate that these intakes were associated with hypercalcaemia in infants.

3.5.6. Vitamin D intake and hypercalcaemia in children and adolescents

Two intervention studies on the effects of vitamin D supplementation on calcaemia in children and adolescents from the same geographical area are available in the literature.

In a randomised “pilot” study, boys and girls aged 10-17 years received for eight weeks starting in August either placebo oil (n=9), weekly amounts of 350 µg vitamin D₃ as oily preparation (n=8) or the same amount of vitamin D₃ dissolved in ethanol (n=9). After eight weeks, two boys in the placebo group had elevated serum calcium concentrations, and one girl who had received vitamin D₃ dissolved in ethanol had high concentrations of both serum 25(OH)D and serum calcium (195 nmol/L and 2.7 mmol/L, respectively). As serum calcium only slightly exceeded the upper limit of normal for that age (2.68 mmol/L), the authors did not consider this as evidence for vitamin D intoxication. Two other subjects with high 25(OH)D concentrations (>150 nmol/L) did not have concomitantly elevated serum calcium concentrations (Maalouf et al., 2008).

In a second study by the same authors, healthy girls (n=168) and boys (n=172) aged 10-17 years from Beirut (latitude 33.5° North) randomly received weekly either 35 µg vitamin D₃ (equivalent to 5 µg/day), 350 µg vitamin D₃ (equivalent to 50 µg/day) or placebo for one year (El-Hajj Fuleihan et al., 2006; Maalouf et al., 2008). The primary outcomes were changes in lean mass, bone mineral density and bone mineral content. Hypercalcaemia did not occur in the girls who received vitamin D₃. Three girls (5 %) in the high-dose group had high serum 25(OH)D concentrations at the end of the study (257, 402 and 487 nmol/L), but none had concomitant hypercalcaemia (>2.68 mmol/L). Two boys (4 %) in the high-dose group had high serum 25(OH)D concentrations at the end of the study (157 and 172 nmol/L), but none had concomitant hypercalcaemia. Five boys, of whom three had received placebo, one the low and one the high vitamin D dose, had hypercalcaemia. Thus, as cases of hypercalcaemia occurred in active and non-active treatment groups, these cases cannot be related to supplementation with vitamin D *per se*. Calcium intake and sun exposure, but not dietary intake of

vitamin D, were measured at baseline and follow-up, but were not reported in relation to adverse events.

The Panel notes that there are only two studies on weekly vitamin D supplementation equivalent to daily intakes of 5-50 µg in children and adolescents, and that the mild hypercalcaemia observed in a few subjects could not be attributed to vitamin D supplementation. The Panel concludes that vitamin D intakes at doses up to 50 µg/day do not lead to hypercalcaemia in children and adolescents aged 10-17 years.

4. Dose-response assessment and derivation of a Tolerable Upper Intake Level

The critical effect of excess intake of vitamin D leading to hypervitaminosis D or vitamin D toxicity is hypercalcaemia. Hypercalciuria can be associated with hypercalcaemia, but it can also occur without.

4.1. Adults

Doses of 234-275 µg vitamin D₃/day were administered in two studies to 10-15 healthy men for eight weeks to about five months without reported hypercalcaemia (Barger-Lux et al., 1998; Heaney et al., 2003). The Panel considers that a daily vitamin D dose of 250 µg/day (range 234-275 µg/day) reflects a NOAEL. The Panel notes that there are a number of uncertainties on whether this estimate of the NOAEL covers the range of variation in the sensitivity of the population to possible adverse effects of vitamin D over the long term and that it is based only on two studies of short duration (up to five months) in small samples of healthy young men with minimal sun exposure. The Panel considers that an uncertainty factor of 2.5 is appropriate to take into account these uncertainties.

Based on a NOAEL of 250 µg/day (range 234-275 µg/day) and the use of an uncertainty factor of 2.5, the UL for adults is estimated at 100 µg/day. Supportive evidence for a UL of 100 µg/day is provided by randomised controlled studies in which this dose or higher doses were administered to various population groups (whites, African Americans, pre- and postmenopausal women, elderly nursing home residents, overweight and obese adults, pregnant and lactating women) for up to 12 months without evidence of (persisting) hypercalcaemia or hypercalciuria.

4.2. Pregnant and lactating women

There is no evidence that pregnancy or lactation increase the susceptibility for adverse effects of vitamin D intake. The Panel considers that the UL of 100 µg/day for adults also applies to pregnant and lactating women. This UL is supported by two studies in pregnant and lactating women, both using doses of vitamin D₂ or D₃ up to 100 µg/day for several weeks to months, which did not report adverse events for either the mothers or their offspring (Hollis and Wagner, 2004; Hollis et al., 2011).

4.3. Infants

For infants, there is still a paucity of data on which to base a NOAEL or a lowest observed adverse effect level (LOAEL). The inconsistent evidence on linear growth from two rather old studies with low numbers of infants has been complemented by retrospective data on linear growth from infants in Finland (Hyppönen et al., 2011). Other studies on the relationship between vitamin D intake and linear growth in infants were not available.

No new data from intervention studies on hypercalcaemia in healthy infants have emerged since the risk assessment undertaken by the SCF in 2003.

Considering the limited evidence that has become available since the last risk assessment (SCF, 2003), the Panel considers that the UL of 25 µg vitamin D/day previously derived for infants from 0-12 months of age should be retained.

4.4. Children and adolescents

Since the previous risk assessment (SCF, 2003), two studies in children aged 10-17 years have become available (El-Hajj Fuleihan et al., 2006; Maalouf et al., 2008). These studies show that vitamin D intakes at doses up to 50 µg/day do not lead to hypercalcaemia in children and adolescents aged 10-17 years. While there are no studies at higher intakes, the Panel considers that there is no reason to believe that adolescents in the phase of rapid bone formation and growth have a lower tolerance for vitamin D compared to adults. Thus, the Panel proposes a UL for vitamin D of 100 µg/day for adolescents aged 11-17 years.

For children aged 1-10 years, no new data from intervention studies have emerged since the last risk assessment (SCF, 2003). The Panel considers that there is no reason to believe that children aged 1-10 years in the phase of rapid bone formation and growth have a lower tolerance for vitamin D compared to adults, and proposes a UL for vitamin D of 50 µg/day by taking into account their smaller body size.

4.5. Summary of Tolerable Upper Intake Levels for vitamin D

| Age (years) | Tolerable Upper Intake Level (UL) for vitamin D (µg/day) |
|-------------------------------|--|
| Children | |
| 0-1 | 25 |
| 1-10 | 50 |
| 11-17 | 100 |
| Adults¹ ≥18 | 100 |

¹ The UL for adults also applies to pregnant and lactating women.

5. Characterisation of the risk

Data from European populations indicate that vitamin D intakes from all sources in high consumers are below the UL for all population subgroups (i.e., about 25 %, 75 %, 30 % and 8 % of the UL for adults, infants, children and adolescents, respectively).

CONCLUSIONS

The UL for vitamin D for adults, including pregnant and lactating women, has been established at 100 µg/day. For children and adolescents, the UL has been set at 50 µg/day for ages 1-10 years, and at 100 µg/day for ages 11-17 years. For infants up to one year of age, the UL is 25 µg/day.

Data from European populations indicate that vitamin D intakes from all sources in high consumers are below the UL for all population subgroups.

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APPENDICES

A. INTAKE OF VITAMIN D AMONG ADULTS IN EUROPEAN COUNTRIES

| Nutrient source | Sex | Country | Reference | Dietary assessment method | n | Age min (years) | Age max (years) | Population / Fortified foods included or excluded | Mean | Median | P75 | P95 | P97.5 |
|-----------------|-------|---------|-------------------------|--|-------|-----------------|-----------------|---|------|--------|-----|------|-------|
| Foods | Women | Austria | (Elmadfa et al., 2009b) | 24-hour recall | 426 | < 25 | > 35 | Pregnant women in 2nd trimester | 2.5 | | | | |
| | | | | | 76 | < 25 | 25 | Pregnant women in 2nd trimester | 2.1 | | | | |
| | | | | | 288 | 25 | 35 | Pregnant women in 2nd trimester | 2.6 | | | | |
| | | | | | 62 | 35 | > 35 | Pregnant women in 2nd trimester | 3.3 | | | | |
| | | Denmark | (Pedersen et al., 2010) | 7-day record (data collected in 2003-2008) | 150 | 18 | 24 | | 2.6 | | | 7.0 | |
| | | | | | 340 | 25 | 34 | | 2.8 | | | 7.6 | |
| | | | | | 412 | 35 | 44 | | 2.9 | | | 8.6 | |
| | | | | | 359 | 45 | 54 | | 3.1 | | | 9.1 | |
| | | | | | 326 | 55 | 64 | | 3.4 | | | 8.4 | |
| | | | | | 198 | 65 | 75 | | 3.4 | | | 8.5 | |
| | | | (Tetens et al., 2011) | 7-day record and interview (data collected in 2000-2004) | 671 | 18 | 49 | Non-supplement users | 2.0 | | | 7.3 | |
| | | | | | 825 | 18 | 49 | Supplements users | 2.1 | | | 7.7 | |
| | | | | | 280 | 50 | 75 | Non-supplement users | 2.3 | | | 7.7 | |
| | | | | | 599 | 50 | 75 | Supplements users | 2.5 | | | 7.9 | |
| | | Finland | (Paturi et al., 2008) | 48-hour recall and two 3-day records for the usual intakes over the past year (assessment of underreporters) | 641 | 25 | 74 | Usual intakes. Underreporters excluded | 6.0 | | | 10.8 | |
| | | Germany | (MRI, 2008) | 24-hour recall + Dietary History | 510 | 19 | 24 | | 2.0 | | | 4.8 | |
| | | | | | 972 | 25 | 34 | | 2.6 | | | 6.4 | |
| | | | | | 2,694 | 35 | 50 | | 2.7 | | | 6.3 | |
| | | | | | 1,840 | 51 | 64 | | 3.4 | | | 8.8 | |
| | | | | | 1,562 | 65 | 80 | | 3.4 | | | 8.2 | |
| | | Ireland | (IUNA, 2011) | 4-day record | 255 | 18 | 35 | | 2.4 | | | 5.8 | 7.9 |
| | | | | | 232 | 36 | 50 | | 2.8 | | | 7.4 | 8.5 |
| | | | | | 153 | 51 | 64 | | 3.3 | | | 8.1 | 10.1 |

| Nutrient source | Sex | Country | Reference | Dietary assessment method | n | Age min (years) | Age max (years) | Population / Fortified foods included or excluded | Mean | Median | P75 | P95 | P97.5 |
|-----------------|-------|-----------------|----------------------------|--|-------|-----------------|-----------------|---|------|--------|-----|------|-------|
| Foods | Women | Italy | (Sette et al., 2010) | Consecutive 3-day food record | 1,245 | 18 | < 65 | Including fortified food | 2.3 | | | 7.3 | |
| | | | | | 316 | 65 | 99 | Including fortified food | 1.8 | | | 6.2 | |
| | | Poland | (Flynn et al., 2009) | 24-hour recall | 1,656 | 18 | 96 | | 3.3 | | | 7.9 | |
| | | Spain | (Flynn et al., 2009) | Two non-consecutive 24-hour recalls (one for all, a second for 62 % of the sample) | 895 | 18 | 64 | Data collected in Catalonia. | 1.1 | | | 2.4 | |
| | | Sweden | (Becker and Pearson, 2002) | 7-day record | 67 | 17 | 24 | | 4.1 | | | 7.6 | |
| | | | | | 128 | 25 | 34 | | 4.5 | | | 7.5 | |
| | | | | | 143 | 35 | 44 | | 4.7 | | | 8.1 | |
| | | | | | 118 | 45 | 54 | | 5.0 | | | 9.1 | |
| | | | | | 68 | 55 | 64 | | 5.8 | | | 9.8 | |
| | | | | | 65 | 65 | 74 | | 6.1 | | | 10.6 | |
| | | The Netherlands | (van Rossum et al., 2011) | Two non-consecutive 24-hour dietary recalls | 347 | 19 | 30 | | | 2.6 | | 4.9 | |
| | | | | | 351 | 31 | 50 | | | 2.8 | | 5.3 | |
| | | | | | 353 | 51 | 69 | | | 3.2 | | 5.8 | |
| Foods | Men | Denmark | (Pedersen et al., 2010) | 7-day record (data collected in 2003-2008) | 105 | 18 | 24 | | 2.6 | | | 5.9 | |
| | | | | | 234 | 25 | 34 | | 3.5 | | | 8.6 | |
| | | | | | 318 | 35 | 44 | | 3.8 | | | 10.4 | |
| | | | | | 336 | 45 | 54 | | 3.7 | | | 9.9 | |
| | | | | | 336 | 55 | 64 | | 4.4 | | | 11.5 | |
| | | | | | 240 | 65 | 75 | | 3.9 | | | 9.9 | |
| | | | (Tetens et al., 2011) | 7-day record and interview (data collected in 2000-2004) | 663 | 18 | 49 | Non supplement users | 2.7 | | | n.a. | |
| | | | | | 587 | 18 | 49 | Supplements users | 2.8 | | | 9.5 | |
| | | | | | 363 | 50 | 75 | Non supplement users | 2.9 | | | 9.4 | |
| | | | | | 491 | 50 | 75 | Supplements users | 3.1 | | | 9.8 | |

| Nutrient source | Sex | Country | Reference | Dietary assessment method | n | Age min (years) | Age max (years) | Population / Fortified foods included or excluded | Mean | Median | P75 | P95 | P97.5 |
|-----------------|-----|-----------------|----------------------------|--|-------|-----------------|-----------------|---|------|--------|-----|------|-------|
| Foods | Men | Finland | (Paturi et al., 2008) | 48-hour recall and two 3-day records for the usual intakes over the past year (assessment of underreporters) | 637 | 25 | 74 | Usual intakes. Underreporters excluded | 8.2 | | | 16.0 | |
| | | | | | | | | | | | | | |
| | | Germany | (MRI, 2008) | 24-hour recall + Dietary History | 510 | 19 | 24 | | 3.0 | | | 7.0 | |
| | | | | | 690 | 25 | 34 | | 3.5 | | | 8.0 | |
| | | | | | 2,079 | 35 | 50 | | 3.8 | | | 9.7 | |
| | | | | | 1,633 | 51 | 64 | | 4.2 | | | 10.9 | |
| | | | | | 1,469 | 65 | 80 | | 4.4 | | | 10.6 | |
| | | Ireland | (IUNA, 2011) | 4-day record | 276 | 18 | 35 | | 3.1 | | | 7.8 | 9.0 |
| | | | | | 205 | 36 | 50 | | 3.4 | | | 8.3 | 9.8 |
| | | | | | 153 | 51 | 64 | | 4.1 | | | 10.8 | 15.6 |
| | | Italy | (Sette et al., 2010) | Consecutive 3-day food record | 1,068 | 18 | < 65 | Including fortified food | 2.6 | | | 7.7 | |
| | | | | | 202 | 65 | 99 | | 2.5 | | | 7.5 | |
| | | Poland | (Flynn et al., 2009) | 24-hour recall | 1,324 | 18 | 96 | | 5.7 | | | 14.8 | |
| | | Spain | (Flynn et al., 2009) | Two non-consecutive 24-hour recalls (one for all, a second for 62 % of the sample) | 718 | 18 | 64 | Data collected in Catalonia. | 1.5 | | | 3.1 | |
| | | Sweden | (Becker and Pearson, 2002) | 7-day record | 67 | 17 | 24 | | 5.6 | | | 11.1 | |
| | | | | | 128 | 25 | 34 | | 5.6 | | | 9.8 | |
| | | | | | 143 | 35 | 44 | | 6.1 | | | 11.3 | |
| | | | | | 118 | 45 | 54 | | 6.6 | | | 12.1 | |
| | | | | | 68 | 55 | 64 | | 6.6 | | | 13.2 | |
| | | The Netherlands | (van Rossum et al., 2011) | Two non-consecutive 24-hour dietary recalls | 65 | 65 | 74 | | 7.1 | | | 12.1 | |
| | | | | | 356 | 19 | 30 | | | 3.5 | | 6.1 | |
| | | | | | 348 | 31 | 50 | | | 3.8 | | 6.6 | |
| | | | | | 351 | 51 | 69 | | | 4.1 | | 7.0 | |

| Nutrient source | Sex | Country | Reference | Dietary assessment method | n | Age min (years) | Age max (years) | Population / Fortified foods included or excluded | Mean | Median | P75 | P95 | P97.5 | | | |
|-----------------------|---------------|-------------|-----------------------|--|-------------------------|--|-----------------|---|----------------------------------|--|--------------------------------|------|--------------------------------|------|------|--|
| Foods | Men and women | France | (Dufour et al., 2010) | 7-day record | 1,918 | 18 | 79 | Non under-reporters. Fortified food excluded. | 2.6 | | | 5.5 | 6.7 | | | |
| | | Ireland | (IUNA, 2011) | 4-day record | 226 | 65 | > 65 | | 3.8 | | | 9.4 | 12.0 | | | |
| | | Portugal | (Lopes et al., 2006) | Food frequency questionnaire | 478 | 18 | 39 | Data collected in Porto | 3.7 | | | 6.6 | | | | |
| | | | | | 537 | 40 | 49 | | 3.6 | | | 6.3 | | | | |
| | | | | | 789 | 50 | 64 | | 3.7 | | | 6.4 | | | | |
| | | | | | 585 | 65 | > 65 | | 3.3 | | | 6.1 | | | | |
| | | | | | 807 | 19 | 64 | | 2.9 | | | | 8.5 | | | |
| | | 224 | 65 | > 65 | | 3.3 | | | | 9.0 | | | | | | |
| | | Supplements | Women | Austria | (Elmadfa et al., 2009b) | Quantitative consumption frequency questionnaire | 22 | 18 | 65 | Assessment of supplement consumption among 282 adults in all Austria (77 supplement users) | | 5.0 | 5.0 | | | |
| | | | | Germany | (MRI, 2008) | 24-hour recall + Dietary History | 18 | 19 | 24 | Users of vitamin D supplements | 5.5 | | | 25.1 | | |
| 48 | 25 | | | | | | 34 | Users of vitamin D supplements | 5.4 | | | 20.0 | | | | |
| 134 | 35 | | | | | | 50 | Users of vitamin D supplements | 5.3 | | | 15.0 | | | | |
| 135 | 51 | | | | | | 64 | Users of vitamin D supplements | 7.3 | | | 22.0 | | | | |
| 136 | 65 | | | | | | 80 | Users of vitamin D supplements | 7.7 | | | 22.0 | | | | |
| Supplements | Men | | | Austria | (Elmadfa et al., 2009b) | Quantitative consumption frequency questionnaire | 15 | 18 | 65 | Assessment of the consumption of supplements among 282 adults in all Austria (77 supplement users) | | 2.0 | 5.0 | | | |
| | | | | | | | Germany | (MRI, 2008) | 24-hour recall + Dietary History | 17 | 19 | 24 | Users of vitamin D supplements | 4.2 | | |
| | | 34 | 25 | | | | | | | 34 | Users of vitamin D supplements | 2.9 | | | 5.0 | |
| | | 90 | 35 | | | | | | | 50 | Users of vitamin D supplements | 4.1 | | | 10.0 | |
| | | 60 | 51 | | | | | | | 64 | Users of vitamin D supplements | 8.5 | | | 15.0 | |
| | | 62 | 65 | | | | | | | 80 | Users of vitamin D supplements | 5.9 | | | 15.0 | |
| Foods and supplements | Women | Denmark | (Tetens et al., 2011) | 7-day record and interview (data collected in 2000-2004) | 825 | 18 | 49 | Supplements users | 7.6 | | | 15.0 | | | | |
| | | | | | 599 | 50 | 75 | Supplements users | 8.3 | | | 17.0 | | | | |

| Nutrient source | Sex | Country | Reference | Dietary assessment method | n | Age min (years) | Age max (years) | Population / Fortified foods included or excluded | Mean | Median | P75 | P95 | P97.5 |
|-----------------------|-------|-----------------|---------------------------|--|-----|-----------------|-----------------|--|------|--------|-----|------|-------|
| Foods and supplements | Women | Finland | (Paturi et al., 2008) | 48-hour recall and two 3-day records for the usual intakes over the past year (assessment of underreporters) | 641 | 25 | 74 | Usual intakes. Underreporters excluded | 8.3 | | | 16.2 | |
| | | Ireland | (IUNA, 2011) | 4-day record | 255 | 18 | 35 | | 3.1 | | | 8.3 | 11.8 |
| | | | | | 232 | 36 | 50 | | 3.5 | | | 9.3 | 13.7 |
| | | | | | 153 | 51 | 64 | | 6.0 | | | 21.3 | 22.6 |
| | | Norway | (Johansson et al., 1998) | Food frequency questionnaire | 406 | 16 | 79 | First quartile of n-3 long-chain polyunsaturated fatty acid intakes | 5.3 | | | | |
| | | | | | 406 | 16 | 79 | Fourth quartile of n-3 long-chain polyunsaturated fatty acid intakes | 18.5 | | | | |
| | | The Netherlands | (van Rossum et al., 2011) | Two non-consecutive 24-hour dietary recalls | 347 | 19 | 30 | | | 2.9 | | 6.3 | |
| | | | | | 351 | 31 | 50 | | | 3.3 | | 7.9 | |
| | | | | | 353 | 51 | 69 | | | 3.8 | | 8.7 | |
| | | | | | | | | | | | | | |
| Foods and supplements | Men | Denmark | (Tetens et al., 2011) | 7-day record and interview | 587 | 18 | 49 | Supplements users | 7.8 | | | 16.0 | |
| | | | | | 491 | 50 | 75 | Supplements users | 8.4 | | | 16.0 | |
| | | Finland | (Paturi et al., 2008) | 48-hour recall and two 3-day records for the usual intakes over the past year (assessment of underreporters) | 637 | 25 | 74 | Usual intakes. Underreporters excluded | 9.5 | | | 18.6 | |
| | | Ireland | (IUNA, 2011) | 4-day record | 276 | 18 | 35 | | 3.9 | | | 10.4 | 13.6 |
| | | | | | 205 | 36 | 50 | | 4.7 | | | 12.1 | 16.9 |
| | | | | | 153 | 51 | 64 | | 5.7 | | | 17.1 | 24.0 |
| | | Norway | (Johansson et al., 1998) | Food frequency questionnaire | 379 | 16 | 79 | First quartile of n-3 long-chain polyunsaturated fatty acid intakes | 5.1 | | | | |
| | | | | | 378 | 16 | 79 | Fourth quartile of n-3 long-chain polyunsaturated fatty acid intakes | 23.5 | | | | |

| Nutrient source | Sex | Country | Reference | Dietary assessment method | n | Age min (years) | Age max (years) | Population / Fortified foods included or excluded | Mean | Median | P75 | P95 | P97.5 |
|-----------------------|---------------|-----------------|---------------------------|---|-----|-----------------|-----------------|---|------|--------|-----|------|-------|
| Foods and supplements | Men | The Netherlands | (van Rossum et al., 2011) | Two non-consecutive 24-hour dietary recalls | 356 | 19 | 30 | | | 3.7 | | 6.7 | |
| | | | | | 348 | 31 | 50 | | | 4.2 | | 8.0 | |
| | | | | | 351 | 51 | 69 | | | 4.4 | | 8.5 | |
| Foods and supplements | Men and women | Ireland | (IUNA, 2011) | 4-day record | 226 | 65 | > 65 | | 6.9 | | | 24.2 | 29.3 |
| | | United Kingdom | (Bates et al., 2011) | 4-day record | 807 | 19 | 64 | | 3.7 | | | | 12.0 |
| | | | | | 224 | 65 | > 65 | | 4.7 | | | | 14.9 |

NB: white lines indicate data for the age-range approximately 19-50 years; grey lines indicate data for the age-range approximately 51 years and over.

n.a.: not available.

B. INTAKE OF VITAMIN D AMONG CHILDREN IN EUROPEAN COUNTRIES

| Nutrient source | Sex | Country | Reference | Dietary assessment method | n | Age min (years) | Age max (years) | Population / Fortified foods included or excluded | Mean | Median | P75 | P90 | P95 | P97.5 |
|-----------------------|----------------|-----------------|------------------------------|---|-------|-----------------|-----------------|--|------|--------|------|------|------|-------|
| Foods and supplements | Girls | Finland | (Kyttälä et al., 2008; 2010) | 3-day record | 198 | 1 | 1 | Non-breast-fed infants, genetically at-risk of type 1 diabetes | 12.2 | | 15.0 | | | |
| Foods and supplements | Boys | Finland | (Kyttälä et al., 2008; 2010) | 3-day record | 257 | 1 | 1 | Non-breast-fed infants, genetically at-risk of type 1 diabetes | 12.2 | | 15.1 | | | |
| Foods and supplements | Boys and girls | The Netherlands | (de Boer et al., 2006) | 2-day record (independent days) | 55 | 0.75 | 0.75 | Supplement users | 12.5 | | | 19.3 | | |
| | | | | | 145 | 1 | 1 | Supplement users | 8.9 | | | 14.8 | | |
| Foods | Girls | Denmark | (Andersen et al., 1996) | 7-day record | 149 | 1 | 3 | | 1.8 | | | | 3.2 | |
| | | The Netherlands | (Ocke et al., 2008) | 2-day record (independent days) | 313 | 2 | 3 | | 1.8 | | | | 3.3 | |
| Foods | Boys | Denmark | (Andersen et al., 1996) | 7-day record | 129 | 1 | 3 | | 1.7 | | | | 2.4 | |
| | | The Netherlands | (Ocke et al., 2008) | 2-day record (independent days) | 327 | 2 | 3 | | 1.8 | | | | 3.0 | |
| Foods | Boys and girls | Greece | (Manios et al., 2008) | 3-day record (weighed food records and 24 h recall or food diaries) | 2,317 | 1 | 5 | Non-under-reporters. Possible inclusion of supplements not mentioned | 5.6 | | | 11.9 | | |
| | | Italy | (Sette et al., 2010) | Consecutive 3-day food records | 52 | 0 | < 3 | Including fortified food | 1.8 | | | | 5.4 | |
| | | United Kingdom | (Bates et al., 2011) | 4-day food diary | 219 | 1.5 | 3 | | 1.9 | | | | | 10.6 |
| Foods and supplements | Girls | Finland | (Kyttälä et al., 2008; 2010) | 3-day record | 118 | 2 | 2 | Genetically at-risk children of type 1 diabetes | 9.0 | | 12.6 | | | |
| | | | | | 235 | 3 | 3 | | 6.9 | | 10.0 | | | |
| | | The Netherlands | (Ocke et al., 2008) | 2-day record (independent days) | 313 | 2 | 3 | | 4.7 | | | | 10.0 | |
| Foods and supplements | Boys | Finland | (Kyttälä et al., 2008; 2010) | 3-day record | 112 | 2 | 2 | Genetically at-risk children of type 1 diabetes | 8.7 | | 11.7 | | | |
| | | | | | 236 | 3 | 3 | | 7.1 | | 9.5 | | | |
| | | The Netherlands | (Ocke et al., 2008) | 2-day record (independent days) | 327 | 2 | 3 | | 4.4 | | | | 8.7 | |
| Foods and supplements | Boys and girls | The Netherlands | (de Boer et al., 2006) | 2-day record (independent days) | 251 | 1.5 | 1.5 | Supplement users | 6.7 | | | 8.1 | | |
| | | United Kingdom | (Bates et al., 2011) | 4-day food diary | 219 | 1.5 | 3 | | 2.3 | | | | | 11.8 |

| Nutrient source | Sex | Country | Reference | Dietary assessment method | n | Age min (years) | Age max (years) | Population / Fortified foods included or excluded | Mean | Median | P75 | P90 | P95 | P97.5 |
|-----------------------|----------------|-----------------|---|---|-------|-----------------|-----------------|---|------|--------|-----|-----|-----|-------|
| Foods | Girls | Ireland | (IUNA (Irish Universities Nutrition Alliance), a) | 7-day record | 301 | 5 | 12 | | 1.6 | | | | 4.4 | 5.2 |
| | | The Netherlands | (van Rossum et al., 2011) | Two non-consecutive 24-hour dietary recalls | 151 | 7 | 8 | | | 2.3 | | | 4.4 | |
| | | | | | 352 | 9 | 13 | | | 2.3 | | | 4.5 | |
| Foods | Boys | Ireland | (IUNA (Irish Universities Nutrition Alliance), a) | 7-day record | 293 | 5 | 12 | | 1.4 | | | | 3.7 | 4.4 |
| | | The Netherlands | (van Rossum et al., 2011) | Two non-consecutive 24-hour dietary recalls | 153 | 7 | 8 | | | 2.3 | | | 4.3 | |
| | | | | | 351 | 9 | 13 | | | 2.7 | | | 5.0 | |
| Foods | Boys and girls | Denmark | (Pedersen et al., 2010) | 7-day record | 903 | 4 | 14 | | 2.3 | | | | 5.9 | |
| | | Italy | (Sette et al., 2010) | Consecutive 3-day food records | 52 | 3 | < 10 | Including fortified food | 2.0 | | | | 5.1 | |
| | | Germany | (Flynn et al., 2009) | 3-day record | 1,234 | 6 | 11 | | 1.8 | | | | 4.0 | |
| | | Poland | (Flynn et al., 2009) | 24-hour recall | 455 | 4 | 10 | | 2.3 | | | | 5.9 | |
| | | Spain | (Flynn et al., 2009) | 24-hour recall and food frequency questionnaire, a second 24-hour recall in 25-30 % of the sample | 723 | 4 | 10 | | 1.4 | | | | 2.9 | |
| | | The Netherlands | (Flynn et al., 2009) | 2-day record (independent days) | 639 | 4 | 6 | Including fortified foods | 1.9 | | | | 3.1 | |
| | | United Kingdom | (Bates et al., 2011) | 4-day food diary | 423 | 4 | 10 | | 1.9 | | | | | 4.1 |
| Foods and supplements | Girls | Finland | (Kyttilä et al., 2008; 2010) | 3-day record | 247 | 4 | 4 | Genetically at-risk children of type 1 diabetes | 6.1 | | 8.3 | | | |
| | | | | | 349 | 6 | 6 | | 5.5 | | 6.6 | | | |
| | | The Netherlands | (van Rossum et al., 2011) | Two non-consecutive 24-hour dietary recalls | 151 | 7 | 8 | | | 2.5 | | | 5.8 | |
| | | | | | 352 | 9 | 13 | | | 2.5 | | | 5.5 | |
| Foods and supplements | Boys | Finland | (Kyttilä et al., 2008; 2010) | 3-day record | 307 | 4 | 4 | Genetically at-risk children of type 1 diabetes | 5.9 | | 7.7 | | | |
| | | | | | 364 | 6 | 6 | | 6.3 | | 7.7 | | | |

| Nutrient source | Sex | Country | Reference | Dietary assessment method | n | Age min (years) | Age max (years) | Population / Fortified foods included or excluded | Mean | Median | P75 | P90 | P95 | P97.5 |
|-----------------------|----------------|-----------------|---|---|-------|-----------------|-----------------|--|------|--------|-----|-----|------|-------|
| Foods and supplements | Boys | The Netherlands | (van Rossum et al., 2011) | Two non-consecutive 24-hour dietary recalls | 153 | 7 | 8 | | | 2.8 | | | 6.3 | |
| | | | | | 351 | 9 | 13 | | | 3.0 | | | 6.3 | |
| Foods and supplements | Boys and girls | Germany | (Flynn et al., 2009) | 3-day record | 1234 | 6 | 11 | | 1.8 | | | | 5.0 | |
| | | Ireland | (IUNA (Irish Universities Nutrition Alliance), a) | 7-day record | 594 | 5 | 12 | | 2.3 | | | | 6.4 | |
| | | Spain | (Flynn et al., 2009) | 24-hour recall and food frequency questionnaire, a second 24-hour recall in 25-30 % of the sample | 723 | 4 | 10 | Including fortified food | 1.8 | | | | 3.0 | |
| | | Sweden | (Enghardt-Barbieri et al., 2006) | 4-day record | 590 | 4 | 4 | | 6.6 | | | | 15.4 | |
| | | | | | 889 | 8 | 9 | | 5.0 | | | | 10.4 | |
| | | | | | 1,016 | 11 | 12 | | 4.6 | | | | 10.1 | |
| | | The Netherlands | (Flynn et al., 2009) | 2-day record (independent days) | 639 | 4 | 6 | | 2.6 | | | | 5.3 | |
| | | | | | 639 | 4 | 6 | Including fortified foods | 2.7 | | | | 5.5 | |
| | | United Kingdom | (Bates et al., 2011) | 4-day food diary | 423 | 4 | 10 | | 2.6 | | | | | 7.3 |
| Foods | Girls | Belgium | (Sioen et al., 2007b) | 7-day record | 212 | 13 | 18 | Data collected in the region of Ghent in Flanders. | 2.5 | | | | 4.9 | |
| | | Denmark | (Pedersen et al., 2010) | 7-day record | 134 | 14 | 17 | | 1.9 | | | | 5.0 | |
| | | Ireland | (IUNA (Irish Universities Nutrition Alliance), b) | 7-day record | 217 | 13 | 17 | | 1.8 | | | | 4.5 | 6.0 |
| | | Italy | (Sette et al., 2010) | Consecutive 3-day food records | 139 | 10 | < 18 | Including fortified food | 2.4 | | | | 6.7 | |
| | | The Netherlands | (van Rossum et al., 2011) | Two non-consecutive 24-hour dietary recalls | 354 | 14 | 18 | | | 2.4 | | | 4.6 | |

| Nutrient source | Sex | Country | Reference | Dietary assessment method | n | Age min (years) | Age max (years) | Population / Fortified foods included or excluded | Mean | Median | P75 | P90 | P95 | P97.5 |
|------------------------------|-----------------------|------------------------|---|---|-------|-----------------|-----------------|--|------|--------|-----|-----|-----|-------|
| Foods | Boys | Belgium | (Sioen et al., 2007b) | 7-day record | 129 | 13 | 18 | Data collected in the region of Ghent in Flanders. | 4.05 | | | | 7.6 | |
| | | Denmark | (Pedersen et al., 2010) | 7-day record | 101 | 14 | 17 | | 3.0 | | | | 6.8 | |
| | | Ireland | (IUNA (Irish Universities Nutrition Alliance), b) | 7-day record | 224 | 13 | 17 | | 2.4 | | | | 6.0 | 7.5 |
| | | Italy | (Sette et al., 2010) | Consecutive 3-day food records | 108 | 10 | < 18 | Including fortified food | 2.6 | | | | 7.7 | |
| | | The Netherlands | (van Rossum et al., 2011) | Two non-consecutive 24-hour dietary recalls | 352 | 14 | 18 | | | 3.1 | | | 5.5 | |
| Foods | Boys and girls | Germany | (Flynn et al., 2009) | 3-day record | 1,272 | 12 | 17 | | 2.4 | | | | 5.5 | |
| | | Spain | (Flynn et al., 2009) | 24-hour recall and food frequency questionnaire, a second 24-hour recall in 25-30 % of the sample | 1,137 | 11 | 17 | | 1.6 | | | | 3.0 | |
| | | United Kingdom | (Bates et al., 2011) | 4-day food diary | 453 | 11 | 18 | | 2.1 | | | | | 5.5 |
| Foods and supplements | Girls | The Netherlands | (van Rossum et al., 2011) | Two non-consecutive 24-hour dietary recalls | 354 | 14 | 18 | | | 2.6 | | | 5.4 | |
| Foods and supplements | Boys | The Netherlands | (van Rossum et al., 2011) | Two non-consecutive 24-hour dietary recalls | 352 | 14 | 18 | | | 3.3 | | | 6.1 | |
| Foods and supplements | Boys and girls | Germany | (Flynn et al., 2009) | 3-day record | 1,272 | 12 | 17 | | 2.5 | | | | 6.3 | |
| | | Ireland | (IUNA (Irish Universities Nutrition Alliance), b) | 7-day record | 441 | 13 | 17 | | 2.7 | | | | 7.6 | |
| | | Poland | (Flynn et al., 2009) | 24-hour recall | 581 | 11 | 17 | | 4.0 | | | | 9.7 | |
| | | Spain | (Flynn et al., 2009) | 24-hour recall and food frequency questionnaire, a second 24-hour recall in 25-30 % of the sample | 1,137 | 11 | 17 | Including fortified food | 1.9 | | | | 3.2 | |
| | | United Kingdom | (Bates et al., 2011) | 4-day food diary | 453 | 11 | 18 | | 2.3 | | | | | 6.5 |

NB: First white section: infants. First grey section: ~1-3 years. Second white section: older children. Second grey section: ~adolescents.

C. VITAMIN D INTAKE AND HYPERCALCAEMIA IN ADULTS

| Author | Study Design | Duration | Number at entry and type of subjects | Age range | Sex | Completers | Vitamin D supplement | Ca supplement | Effect Intervention group with highest dose | | Effect Control group | | Hypercalcaemia | Remarks |
|--|---|------------------------------|--|-----------|-------|--------------|--|---------------|--|---|---|---|----------------|---------|
| | | | | | | | | | serum Ca | serum 25(OH)D | serum Ca | serum 25(OH)D | | |
| | | (months) | | (years) | (m/f) | (n) | Equivalent daily dose (µg/day) | (mg/day) | (mmol/L) | (nmol/L) | (mmol/L) | (nmol/L) | (Yes / No) | |
| Zittermann et al., 2009 | Rando- mised, double- blind, placebo- controlled | 12 (starting December) | 200 healthy overweight adults | 18-70 | 62 m | 165 | 83.3 µg vitamin D ₃ /day | No | t ₀ : 2.36±0.08 t ₁₂ : 2.38±0.10 Δ: 0.02±0.09 | t ₀ : 30.0±17.5 t ₁₂ : 85.5±57.5 Δ: 55.5±55.8 | t ₀ : 2.38±0.10 t ₁₂ : 2.40±0.25 Δ: 0.02±0.24 | t ₀ : 30.3±20.1 t ₁₂ : 42.0±35.0 Δ: 11.8±36.3 | No | |
| Bad Oeynhausen, Germany (latitude 52°N) | | | | | | | | | | | | | | |
| Narang et al., 1984 | Inter- vention trial | 3 (season not reported) | 30 healthy adults | 21-60 | both | not reported | 10, 20, 30, 60, or 95 µg vitamin D/day | No | 60 µg D/day: t ₀ : 2.43±0.13 t ₃ : 2.62±0.22 95 µg D/day: t ₀ : 2.46±0.09 t ₃ : 2.83±0.21 | Not reported | 10 µg D/day: t ₀ : 2.4±0.06 t ₃ : 2.5±0.13 | Not reported | Not reported | |
| Ajmer, India (latitude 26°N) | | | | | | | | | | | | | | |

| Author | Study Design | Duration | Number at entry and type of subjects | Age range | Sex | Completers | Vitamin D supplement | Ca supplement | Effect Intervention group with highest dose | | Effect Control group | | Hypercalcaemia | Remarks |
|---------------------------|--|--|---|-----------|-------|-----------------------|---|---------------|--|--|-------------------------|---------------|----------------|---|
| | | | | | | | | | serum Ca | serum 25(OH)D | serum Ca | serum 25(OH)D | | |
| | | (months) | | (years) | (m/f) | (n) | Equivalent daily dose (µg/day) | (mg/day) | (mmol/L) | (nmol/L) | (mmol/L) | (nmol/L) | (Yes / No) | |
| Aloia et al., 2008 | Rando- mised, double- blind, placebo- controlled | 6 (3 successive winters November - March) | 138 white (76) and African- American (62) | 18-65 | both | 111 | Dose of vitamin D ₃ based on initial 25(OH)D concentration and adjusted at week 9 and week 18: dose range up to week 9: 50-100 µg/day, subsequent dose range: 20-170 µg/day, median dose: 95 µg vitamin D ₃ /day | No | t ₆ : < 2.65 | To obtain and maintain serum 25(OH)D >80 nmol/L and < 140 nmol/L throughout the study | t ₆ : < 2.65 | Δ: 19.5±16.0 | No | 4 patients with hypercalciuria on several occasions equally often in vitamin D and placebo group |
| Vieth et al., 2001 | Rando- mised | 5 (starting between January and February) | 73 healthy adults | 18-56 | both | 61 completed ≥1 month | 25 or 100 µg/day D ₃ | No | mean <2.45, all subjects remained within reference range (2.2-2.6) | 100 µg/day: t ₀ : 37.9±13.4 plateau after 3 months at mean (range) of 96 (69-125) | n/a | n/a | No | On a group basis, no change from baseline in urinary molar Ca:creatinine ratios in randomly collected urine samples. In 1 subject on 100 µg/day D ₃ , hypercalciuria occurred in 2 of 6 measurements, but time points not specified. |

| Author | Study Design | Duration | Number at entry and type of subjects | Age range | Sex | Completers | Vitamin D supplement | Ca supplement | Effect Intervention group with highest dose | | Effect Control group | | Hypercalcaemia | Remarks |
|-------------------------------|---------------------------------------|--|--|-----------|-------|------------|---|---|---|--|---|---|---|--|
| | | | | | | | | | serum Ca | serum 25(OH)D | serum Ca | serum 25(OH)D | | |
| | | (months) | | (years) | (m/f) | (n) | Equivalent daily dose (µg/day) | (mg/day) | (mmol/L) | (nmol/L) | (mmol/L) | (nmol/L) | (Yes / No) | |
| | | | | | | | | | | | | | | Relative number of occurrences of hypercalciuria across the entire follow-up period was not different between groups. |
| Tjellesen et al., 1986 | Randomised, double-blind uncontrolled | 8 weeks (September-November) | 19 healthy premenopausal women | 22-49 | f | 19 | 97 µg/day D ₂ or 110 µg/day D ₃ | 500 | 97 µg/day D ₂ : t ₀ : 2.46±0.03 t ₈ : 2.46±0.01 110 µg/day D ₃ : t ₀ : 2.46±0.02 t ₈ : 2.51±0.02, p<0.02, mean±SEM | 97 µg/day D ₂ : t ₀ : 75 (55-96) t ₈ : 89 (49-121) 110 µg/day D ₃ : t ₀ : 77 (46-100) t ₈ : 113 (77-138), median (range) | n/a | n/a | Not reported | |
| Gallagher et al., 2012 | Randomised, placebo-controlled | 12 (screening in 2 successive years in April or January to May, enrollment on average 5 weeks after screening) | 163 healthy postmenopausal white women with 25(OH)D <50 nmol/L | 57-90 | f | 147 | 0, 12.6, 22.8, 38.3, 64.8, 73.7, 105.2, or 123.4 µg/day D ₃ (analysed doses) | Yes, to obtain a total Ca intake of 1,200-1,400 | 105.2 µg/day D ₃ : t ₀ : 2.35±0.1 t ₁₂ : not reported 123.4 µg/day D ₃ : t ₀ : 2.37±0.075 t ₁₂ : not reported | 105.2 µg/day D ₃ : t ₀ : 37.2±9.2 t ₁₂ : 112.9 123.4 µg/day D ₃ : t ₀ : 38.6±9.1 t ₁₂ : 115.0 (Values at 12 months calculated on the basis of the estimated dose-response curve) | t ₀ : 2.37±0.1 t ₁₂ : not reported | t ₀ : 37.7±9.1 t ₁₂ : 54.5 (Values at 12 months calculated on the basis of the estimated dose-response curve) | 5 subjects ≥2.7 mmol/L, 1 in highest dose group, others on 12.6, 22.8, 64.8 µg D ₃ /day. 16 subjects ≥2.5 mmol/L, 2 in highest dose group, rest in all other groups including placebo; all normal at repeat testing within 2 weeks | 19 subjects with hypercalciuria (>400 mg Ca/day), 2 in highest dose group, rest in all other groups including placebo, normal at repeat testing in all but 3 subjects in which Ca or Ca+D ₃ was |

| Author | Study Design | Duration | Number at entry and type of subjects | Age range | Sex | Completers | Vitamin D supplement | Ca supplement | Effect Intervention group with highest dose | | Effect Control group | | Hypercalcaemia | Remarks |
|---|--|------------------------|--------------------------------------|-----------|-------|------------|---|---------------|--|---|---|--|---|--|
| | | | | | | | | | serum Ca | serum 25(OH)D | serum Ca | serum 25(OH)D | | |
| | | (months) | | (years) | (m/f) | (n) | Equivalent daily dose (µg/day) | (mg/day) | (mmol/L) | (nmol/L) | (mmol/L) | (nmol/L) | (Yes / No) | |
| | | | | | | | | | | | | | | then withdrawn |
| Mocanu et al., 2009 Iasi, Romania (latitude 47°N) | Uncontrolled | 12 (November-December) | 45 nursing home residents | 58-89 | both | 40 | 125 µg/day D ₃ via fortified bread | 320 | t ₀ : 2.29±0.15 (2.1-2.65) t ₁₂ : 2.28±0.15 (1.9-2.55) | t ₀ : 28.8±9.9 t ₁₂ : 126.4±37.3 (slightly different values reported in abstract) Δ: 98.0 (median) | n/a | n/a | No | 3 subjects with molar Ca:creatinine ratio >1 on one occasion at 6 or 9 months in the study |
| Jorde et al., 2010 (also described in Sneve et al., 2008) Tromsø, Norway (latitude 69°N) | Randomised, double-blind, placebo-controlled | 12 (starting November) | 438 overweight or obese adults | 21-70 | both | 330 | 0, 71, or 143 µg/day D ₃ | 500 | 71 µg/day D ₃ : t ₀ : 2.32±0.11 Δ: -0.01±0.11 143 µg/day D ₃ : t ₀ : 2.30±0.11 Δ: 0.00±0.12 | 71 µg/day D ₃ : t ₀ : 56.7±21.2 Δ: +42.8±22.5 143 µg/day D ₃ : t ₀ : 58.7±21.2 Δ: +79.3±31.2 | t ₀ : 2.31±0.10 Δ: -0.01±0.11 | t ₀ : 58.8±21.0 Δ: -1.6±16.8 | 3 excluded because of 2 serum measurements >2.6 mmol/L (1 in Ca-only group, 2 in Ca + low D ₃), 4 subjects with transient increase in serum Ca (1 in Ca-only, 3 in Ca + high D ₃) who remained in study | |

| Author | Study Design | Duration | Number at entry and type of subjects | Age range | Sex | Completers | Vitamin D supplement | Ca supplement | Effect Intervention group with highest dose | | Effect Control group | | Hypercalcaemia | Remarks |
|--|--------------------------------------|--|--|-----------|-------|--------------|---|---------------|--|---|--|--|--|--------------------------------|
| | | | | | | | | | serum Ca | serum 25(OH)D | serum Ca | serum 25(OH)D | | |
| | | (months) | | (years) | (m/f) | (n) | Equivalent daily dose (µg/day) | (mg/day) | (mmol/L) | (nmol/L) | (mmol/L) | (nmol/L) | (Yes / No) | |
| Grimnes et al., 2012 | Rando- mised, double- blind | 12 (subjects were asked to report on mean time spent outdoors between 10 AM and 3 PM in March–April and between 8 AM and 8 PM in June–August) | 297 postmeno- pausal women with reduced bone mineral density | 50-80 | f | 275 | 20 or 163 µg/day D ₃ | 1,000 | 20 µg/day D ₃ : t ₀ : 2.36±0.07 Δ: 0.00±0.10 | 20 µg/day D ₃ : t ₀ : 71.2±22.3 Δ: +18.0±18.9 | n/a | n/a | Modest hypercalcaemia (defined as serum calcium of 2.6-2.8 mmol/L) was reported for 9 women in the high-dose group and 4 women in the low-dose group, at serum 25(OH)D concentrations across a range of 64-256 nmol/L, all resolved at retesting | |
| Berlin et al., 1986 (also described in Berlin T and Björckhem I, 1987) | Control- led | 7 weeks (March-April) | 24 healthy Swedish | 22-47 | m | 24 | 193 µg/day D ₃ | No | t ₀ : 2.47±0.03 t ₇ : 2.49±0.03 (mean±SEM) | t ₀ : 38±4 t ₇ : 123±5 (mean±SEM) | t ₀ : 2.50±0.02 t ₇ : 2.44±0.04 (mean±SEM) | t ₀ : 37±2 t ₇ : 48±3 (mean±SEM) | Not reported | No side effects were recorded. |
| Heaney et al., 2003 | Rando- mised, controlled | 20 weeks: (winter months of 2 successive years: late October-late February/early March) | 67 healthy adults | 38.7±11.2 | m | not reported | 0, 20.9, 137.5, or 275 µg/day D ₃ (analysed doses) | No | t ₀ : 2.4, no change from baseline at any time point (1, 3, 6, 10, 20 weeks) for subjects in two highest dose groups | t ₀ : 70.3±19.9 for all subjects 137.5 µg/day: Δ: +91.9±37.6 275 µg/day: Δ: +159.4±62.4 | Not reported | Δ: -11.4±17.7 | No (all 31 subjects in two highest dose groups <2.6 mmol/L) | |

| Author | Study Design | Duration | Number at entry and type of subjects | Age range | Sex | Completers | Vitamin D supplement | Ca supplement | Effect Intervention group with highest dose | | Effect Control group | | Hypercalcaemia | Remarks |
|--------------------------------|------------------------|---|--|-----------|-------|------------|--|-------------------------|--|--|---|---|--|---|
| | | | | | | | | | serum Ca | serum 25(OH)D | serum Ca | serum 25(OH)D | | |
| | | (months) | | (years) | (m/f) | (n) | Equivalent daily dose (µg/day) | (mg/day) | (mmol/L) | (nmol/L) | (mmol/L) | (nmol/L) | (Yes / No) | |
| Rickers et al., 1982 | Randomised, controlled | 24 weeks | 31 patients under treatment with prednisone for various diseases | 27-81 | both | 31 | 321 µg/day D ₂ (in combination with prednisone and 50 mg/day sodium fluoride) | 4,500 calcium phosphate | t ₀ : 2.48±0.05 t ₂₄ : 2.46±0.03 (mean±SEM) | 25(OH)D₂ t ₀ : 4.2±1.2 t ₂₄ : 145.3±19.0 25(OH)D₃ t ₀ : 38.4±4.2 t ₂₄ : 10.2±1.2 (mean±SEM) | t ₀ : 2.50±0.04 t ₂₄ : 2.44±0.05 (mean±SEM) | 25(OH)D₂ t ₀ : 8.7±2.2 t ₂₄ : 7.2±3.5 25(OH)D₃ t ₀ : 42.7±5.5 t ₂₄ : 34.4 ±5.5 (mean±SEM) | Not reported | |
| Hasling et al., 1987 | Uncontrolled | 5 years (mean observation time 2.8 years) | 163 consecutive patients with spinal crush fracture osteoporosis | 16-84 | both | 43 | 450 µg/day D ₂ (in combination with 60 mg/day sodium fluoride) | 1,800 | t ₀ : 2.50±0.1 t _{5y} : 2.45±0.06, p<0.001, no change at 6-12 months (n=152 patients) | levels increased during treatment (reported in Charles et al., 1985) | n/a | n/a | No hypercalcaemic episodes were observed | Urinary Ca excretion did not change during treatment. |
| Barger-Lux et al., 1998 | Open-label | 8 weeks (Jan-April) | 38 healthy | 20-37 | male | 38 | 35, 234, or 1,269 µg/day D ₃ (analysed doses) | No | Not reported | t ₀ in all 116 subjects in study: 67±25 35 µg D ₃ /day: Δ: +28.6±5.3 234 µg D ₃ /day: Δ: +146.1±12.0 1,269 µg D ₃ /day: Δ: +643.0±42.7 (mean±SEM) | n/a | n/a | "no hypercalcaemia was detected in post-treatment testing of our vitamin D ₃ -treated subjects" | |

| Author | Study Design | Duration | Number at entry and type of subjects | Age range | Sex | Completers | Vitamin D supplement | Ca supplement | Effect Intervention group with highest dose | | Effect Control group | | Hypercalcaemia | Remarks |
|-------------------------------------|--------------|-------------------|---|-----------|-------|------------|--------------------------------|-------------------|---|---------------|----------------------|---------------|----------------|---------|
| | | | | | | | | | serum Ca | serum 25(OH)D | serum Ca | serum 25(OH)D | | |
| | | (months) | | (years) | (m/f) | (n) | Equivalent daily dose (µg/day) | (mg/day) | (mmol/L) | (nmol/L) | (mmol/L) | (nmol/L) | (Yes / No) | |
| Schwartzman and Franck, 1987 | Case reports | 6 weeks – 5 years | 4 patients with osteoporosis (3) or osteomalacia (1); 2 of 4 with corticoid therapy; 1 with renal insufficiency | 42-77 | f | n/a | 1,250 µg/? | Yes, dose unknown | 3.35 | 354 | n/a | n/a | Yes | |
| | | | | | | | 179 µg/day D ₂ | Yes, dose unknown | 2.88 | Not reported | | | | |
| | | | | | | | 1,250 µg/day | 400 | 3.75 | 339 | | | | |
| | | | | | | | 357 µg/day D ₂ | 400 | Not reported | 634 | | | | |
| Selby et al., 1995 | Case reports | 10 years | 6 patients with hypoparathyroidism, hypophosphataemic rickets, coeliac disease, paraesthesiae or unknown reason for vitamin D therapy | 51 | both | n/a | 2,500 µg/day | Not reported | 3.19 | 866 | n/a | n/a | Yes | |
| | | 2 years | | 14 | | | 5,000 µg/day | | 3.00 | 802 | | | | |
| | | 10 years | | 47 | | | 2,500 µg/day | | 3.24 | 1005 | | | | |
| | | 13 years | | 52 | | | 2,500 µg/day | | 3.31 | 533 | | | | |
| | | unknown | | 36 | | | unknown | | 3.07 | 643 | | | | |
| | | 2 years | | 57 | | | 5,000 µg/day | | 3.77 | 1203 | | | | |

| Author | Study Design | Duration | Number at entry and type of subjects | Age range | Sex | Completers | Vitamin D supplement | Ca supplement | Effect Intervention group with highest dose | | Effect Control group | | Hypercalcaemia | Remarks |
|--|--------------|---------------|--|-----------|-------|------------|------------------------------------|---|---|---------------|----------------------|---------------|--|---------|
| | | | | | | | | | serum Ca | serum 25(OH)D | serum Ca | serum 25(OH)D | | |
| | | (months) | | (years) | (m/f) | (n) | Equivalent daily dose (µg/day) | (mg/day) | (mmol/L) | (nmol/L) | (mmol/L) | (nmol/L) | (Yes / No) | |
| Davies and Adams, 1978 Manchester, UK (latitude 53°N) | Case reports | Several years | 8 patients with hypoparathyroidism, Paget's disease, vit. D-resistant rickets, osteoporosis, or symptoms suggesting carpal-tunnel syndrome | 59 | both | n/a | 1,250-2,500 µg D ₂ /day | Yes, dose not specified; not reported for all other cases | 3.1 | Not reported | n/a | n/a | Yes | |
| | | 7 years | | 71 | | | 3,750 µg D ₂ /day | | 4.5 | 1,123 | | | | |
| | | 10 years | | 51 | | | 2,500 µg/day | | 3.75 | 998 | | | | |
| | | 4 months | | 55 | | | 3,750 µg/day | | 3.9 | Not reported | | | | |
| | | 3 years | | 60 | | | 1,250 µg/day | | 4.3 | Not reported | | | | |
| | | 2 years | | 15 | | | 5,000 µg/day | | 3.1 | Not reported | | | | |
| | | 9 months | | 30 | | | 1,250 µg/day | | 4.0 | Not reported | | | | |
| | | 10 years | | 44 | | | 2,500 µg/day | | 3.1 | Not reported | | | | |
| Rizzoli et al., 1994 Geneva, Switzerland (latitude 69°N) | Case reports | 96 weeks | 6 patients with osteoporosis, or hypoparathyroidism | 72 | both | n/a | 2,143 µg/day D ₃ | Not reported | 3.55 | 221 | n/a | n/a | Yes, in all but one patient who was considered vitamin D intoxicated on the basis of signs of enhanced bone resorption, history of excessive vit. D intake and increased 25(OH)D concentration | |
| | | 3 weeks | | 56 | | | 7,500 µg/day D ₃ | | 2.83 | 801 | | | | |
| | | 74 weeks | | 50 | | | 7,500 µg/day D ₃ | | 3.30 | 1,692 | | | | |
| | | 12 weeks | | 66 | | | 1,071 µg/day D ₃ | | 2.53 | 374 | | | | |
| | | 4 weeks | | 84 | | | 7,500 µg/day D ₃ | | 4.59 | 650 | | | | |
| | | 4 weeks | | 79 | | | 7,500 µg/day D ₃ | | 3.29 | 621 | | | | |

n/a: not applicable; m: males; f: females

GLOSSARY AND ABBREVIATIONS

| | |
|-------------------------|--|
| 25(OH)D | 25-Hydroxy-vitamin D (sum of 25-Hydroxy-vitamin D ₂ and 25-Hydroxy-vitamin D ₃) |
| 1,25(OH) ₂ D | Active metabolite/vitamin D hormone |
| BMI | Body mass index |
| CI | Confidence interval |
| CYP | Cytochrome P |
| IoM | Institute of Medicine |
| LOAEL | Lowest observed adverse effect level |
| NHANES | United States National Health and Nutrition Examination Survey |
| NOAEL | No observed adverse effect level |
| OR | Odds ratio |
| RCT | Randomised controlled trial |
| SCF | Scientific Committee on Food |
| SEM | Standard error of the mean |
| SGA | Small-for-gestational age |
| UL | Tolerable Upper Intake Level |
| UV | Ultraviolet |
| Vitamin D ₂ | Ergocalciferol (also termed viosterol) |
| Vitamin D ₃ | Cholecalciferol |