SCIENTIFIC OPINION

Scientific Opinion on the Tolerable Upper Intake Level of vitamin D[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

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

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 D_2 or D_3 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).

TABLE OF CONTENTS

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 foods[4] or food supplements[5], i.e. cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). 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 D_2 or vitamin D_3 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 D_2. Animal foods such as fatty fish, liver, fish liver oils and egg yolks contain vitamin D_3. 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 D_3. Previtamin D_3 thermally isomerises to vitamin D_3 immediately after formation. Sunlight itself regulates the total production of vitamin D_3 in the skin, as both previtamin D_3 and vitamin D_3 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 P_{450} (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 D_2 and vitamin D_3 may equally increase 25(OH)D concentrations when supplemented daily, vitamin D_3 may raise 25(OH)D concentrations more than vitamin D_2 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 D_2 and D_3 metabolites. Plasma 25-hydroxyergocalciferol ($25(OH)D_2$) is of exogenous origin only, while 25-hydroxycholecalciferol ($25(OH)D_3$) 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 D_3 in exposed skin (Holick, 2006). Below a latitude of approximately 35° North, UV-B radiation is sufficient for vitamin D_3 synthesis all year round. At higher latitudes, there is no cutaneous vitamin D_3 synthesis during the winter months. For example, in Rome, Italy (latitude 41.9° North), cutaneous vitamin D_3 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 D_3 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 $24,25(OH)_2D_3$, $25,26(OH)_2D_3$, and $25(OH)D_3$-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 $1,25(OH)_2 D$ 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 persistance 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 D_3/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 D_3/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 D_3-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 D_2/day, 450 µg vitamin D_2/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 D_3/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 D_3/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 µg vitamin D$_3$/day (n=21 studies) or ≥20 µg vitamin D$_2$/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 µg/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 µg/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 µg 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 D_3/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 D_3/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 D_3/day group) attained this threshold without accompanying hypercalcaemia or hypercalciuria.

In another study, lactating women (n=18) randomly received either 40 µg vitamin D_2+10 µg vitamin D_3/day or 90 µg vitamin D_2+10 µg vitamin D_3/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 D_2+10 µg vitamin D_3/day and from 82±6 to 111±10 nmol/L in the group receiving 90 µg vitamin D_2+10 µg vitamin D_3/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 D_2 or D_3 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 D_2) 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 D_2/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 D_2 (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 D_2 daily (n=12), 1,250 μg vitamin D_2 weekly (n=14), or 50 μg vitamin D_3 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 D_2 daily, +3 % for vitamin D_2 weekly, +1 % for vitamin D_3 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 D_3 as oily preparation (n=8) or the same amount of vitamin D_3 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 D_3 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 D_3 (equivalent to 5 μg/day), 350 μg vitamin D_3 (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 D_3. 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 D_3/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 D_2 or D_3 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
Adults[1] ≥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.

REFERENCES

Ala-Houhala M, 1985. 25-Hydroxyvitamin D levels during breast-feeding with or without maternal or infantile supplementation of vitamin D. Journal of Pediatric Gastroenterology and Nutrition, 4, 220-226.

Ala-Houhala M, Koskinen T, Terho A, Koivula T and Visakorpi J, 1986. Maternal compared with infant vitamin D supplementation. Archives of Disease in Childhood, 61, 1159-1163.

Aloia JF, Patel M, Dimaano R, Li-Ng M, Talwar SA, Mikhail M, Pollack S and Yeh JK, 2008. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. American Journal of Clinical Nutrition, 87, 1952-1958.

Andersen N, Fagt S, Groth M, Hartkopp H, Møller A, Ovesen L and Warming D, 1996. Danskernes kostvaner 1995. Hovedresultater [The Danish diet 1995. Main results]. Levnedsmiddelstyrelsen, Søborg, Denmark, 298 pp.

Anderson JL, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, Lappe DL and Muhlestein JB, 2010. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. American Journal of Cardiology, 106, 963-968.

Araki T, Holick MF, Alfonso BD, Charlap E, Romero CM, Rizk D and Newman LG, 2011. Vitamin D intoxication with severe hypercalcemia due to manufacturing and labeling errors of two dietary supplements made in the United States. Journal of Clinical Endocrinology and Metabolism, 96, 3603-3608.

Barger-Lux MJ, Heaney RP, Dowell S, Chen TC and Holick MF, 1998. Vitamin D and its major metabolites: serum levels after graded oral dosing in healthy men. Osteoporosis International, 8, 222-230.

Barger-Lux MJ and Heaney RP, 2002. Effects of above average summer sun exposure on serum 25-hydroxyvitamin D and calcium absorption. Journal of Clinical Endocrinology and Metabolism, 87, 4952-4956.

Barrueto F, Jr., Wang-Flores HH, Howland MA, Hoffman RS and Nelson LS, 2005. Acute vitamin D intoxication in a child. Pediatrics, 116, e453-456.

Bates E, Lennox A, Bates C and Swan G, 2011. National Diet and Nutrition Survey. Headline results from Years 1 and 2 (combined) of the Rolling Programme (2008/2009 - 2009/2010). A Survey carried out on the behalf of the Food Standards Agency and the Department of Health, 68 pp.

Becker W and Pearson M, 2002. Riksmaten 1997-1998. Befolkningens kostvanor och näringsintag. Metod- och resultatanalys [Riksmaten 1997-1998. Dietary habits and nutrient intake in Sweden. Benchmarking analysis]. Livsmedelsverket, 201 pp.

Berlin T, Emtestam L and Björkhem I, 1986. Studies on the relationship between vitamin D3 status and urinary excretion of calcium in healthy subjects: effects of increased levels of 25-hydroxyvitamin D3. Scandinavian Journal of Clinical and Laboratory Investigation, 46, 723-729.

Berlin T and Björkhem I, 1987. Lack of effects of an increased pool of 25-hydroxyvitamin D3 on urinary excretion of calcium in healthy subjects. Contributions to Nephrology, 58, 143-147.

Better OS, Shabtai M, Kedar S, Melamud A, Berenheim J and Chaimovitz C, 1980. Increased incidence of nephrolithiasis (N) in lifeguards (LG) in Israel. Advances in Experimental Medicine and Biology, 128, 467-472.

Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, Bjelakovic M and Gluud C, 2011. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database of Systematic Reviews, CD007470.

Blank S, Scanlon KS, Sinks TH, Lett S and Falk H, 1995. An outbreak of hypervitaminosis D associated with the overfortification of milk from a home-delivery dairy. American Journal of Public Health, 85, 656-659.

Bodnar LM, Catov JM, Zmuda JM, Cooper ME, Parrott MS, Roberts JM, Marazita ML and Simhan HN, 2010. Maternal serum 25-hydroxyvitamin D concentrations are associated with small-for-gestational age births in white women. Journal of Nutrition, 140, 999-1006.

Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, Lieben L, Mathieu C and Demay M, 2008. Vitamin D and human health: lessons from vitamin D receptor null mice. Endocrine Reviews, 29, 726-776.

Cauley JA, Danielson ME, Boudreau R, Barbour KE, Horwitz MJ, Bauer DC, Ensrud KE, Manson JE, Wactawski-Wende J, Shikany JM and Jackson RD, 2011. Serum 25-hydroxyvitamin D and clinical fracture risk in a multiethnic cohort of women: The Women's Health Initiative (WHI). Journal of Bone and Mineral Research, 26, 2378-2388.

Cawthon PM, Parimi N, Barrett-Connor E, Laughlin GA, Ensrud KE, Hoffman AR, Shikany JM, Cauley JA, Lane NE, Bauer DC, Orwoll ES and Cummings SR, 2010. Serum 25-hydroxyvitamin D, parathyroid hormone, and mortality in older men. Journal of Clinical Endocrinology and Metabolism, 95, 4625-4634.

Chel V, Wijnhoven HA, Smit JH, Ooms M and Lips P, 2008. Efficacy of different doses and time intervals of oral vitamin D supplementation with or without calcium in elderly nursing home residents. Osteoporosis International, 19, 663-671.

Chlebowski RT, Johnson KC, Kooperberg C, Pettinger M, Wactawski-Wende J, Rohan T, Rossouw J, Lane D, O'Sullivan MJ, Yasmeen S, Hiatt RA, Shikany JM, Vitolins M, Khandekar J and Hubbell FA, 2008. Calcium plus vitamin D supplementation and the risk of breast cancer. Journal of the National Cancer Institute, 100, 1581-1591.

Chung M, Lee J, Terasawa T, Lau J and Trikalinos TA, 2011. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. Annals of Internal Medicine, 155, 827-838.

Davies M and Adams PH, 1978. The continuing risk of vitamin-D intoxication. Lancet, 2, 621-623.

De-Regil LM, Palacios C, Ansary A, Kulier R and Pena-Rosas JP, 2012. Vitamin D supplementation for women during pregnancy. Cochrane Database of Systematic Reviews, 2, CD008873.

de Boer EJ, Hulshof K and Doest DT, 2006. Voedselconsumptie van jonge peuters [Food consumption of young children]. TNO report V6269, 37 pp.

Deharveng G, Charrondiere UR, Slimani N, Southgate DA and Riboli E, 1999. Comparison of nutrients in the food composition tables available in the nine European countries participating in EPIC. European Prospective Investigation into Cancer and Nutrition. European Journal of Clinical Nutrition, 53, 60-79.

DeLuca HF, Prahl JM and Plum LA, 2011. 1,25-Dihydroxyvitamin D is not responsible for toxicity caused by vitamin D or 25-hydroxyvitamin D. Archives of Biochemistry and Biophysics, 505, 226-230.

Dufour A, Wetzler S, Touvier M, Lioret S, Gioda J, Lafay L, Dubuisson C, Calamassi-Tran G, Kalonji E, Margaritis I and Volatier JL, 2010. Comparison of different maximum safe levels in fortified foods and supplements using a probabilistic risk assessment approach. British Journal of Nutrition, 104, 1848-1857.

Durup D, Jorgensen HL, Christensen J, Schwarz P, Heegaard AM and Lind B, 2012. A Reverse J-Shaped Association of All-Cause Mortality with Serum 25-Hydroxyvitamin D in General Practice, the CopD Study. Journal of Clinical Endocrinology and Metabolism, 97, ahead of print.

Eaton CB, Young A, Allison MA, Robinson J, Martin LW, Kuller LH, Johnson KC, Curb JD, Van Horn L, McTiernan A, Liu S and Manson JE, 2011. Prospective association of vitamin D concentrations with mortality in postmenopausal women: results from the Women's Health Initiative (WHI). American Journal of Clinical Nutrition, 94, 1471-1478.

EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2012. Scientific Opinion on the Tolerable Upper Intake Level of calcium. EFSA Journal, 10(7):2814, 44 pp.

El-Hajj Fuleihan G, Nabulsi M, Tamim H, Maalouf J, Salamoun M, Khalife H, Choucair M, Arabi A and Vieth R, 2006. Effect of vitamin D replacement on musculoskeletal parameters in school children: a randomized controlled trial. Journal of Clinical Endocrinology and Metabolism, 91, 405-412.

Elamin MB, Abu Elnour NO, Elamin KB, Fatourechi MM, Alkatib AA, Almandoz JP, Liu H, Lane MA, Mullan RJ, Hazem A, Erwin PJ, Hensrud DD, Murad MH and Montori VM, 2011. Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. Journal of Clinical Endocrinology and Metabolism, 96, 1931-1942.

Elmadfa I, Freisling H, Nowak V, Hofstädter D, Hasenegger V, Ferge M, Fröhler M, Fritz K, Meyer AL, Putz P, Rust P, Grossgut R, Mischek D, Kiefer I, Schätzer M, Spanblöchel J, Sturtzel B, Wagner K-H, Zilberszac A, Vojir F and Plsek K, 2009b. Österreichischer Ernährungsbericht 2008 [Austrian Nutrition Report 2008]. Institut für Ernährungswissenschaften der Universität Wien, Bundesministerium für Gesundheit, 454 pp.

Enghardt-Barbieri H, Pearson M and Becker W, 2006. Riksmaten – Barn 2003. Livsmedels – och näringsintag bland barn i Sverige [Riksmaten - Children 2003. The food and nutritional intake among children in Sweden]. Livsmedelsverket, 216 pp.

Fiscella K and Franks P, 2010. Vitamin D, race, and cardiovascular mortality: findings from a national US sample. Annals of Family Medicine, 8, 11-18.

Flynn A, Hirvonen T, Mensink GB, Ocke MC, Serra-Majem L, Stos K, Szponar L, Tetens I, Turrini A, Fletcher R and Wildemann T, 2009. Intake of selected nutrients from foods, from fortification and from supplements in various European countries. Food and Nutrition Research, 53, Suppl 1, 1-51.

Fomon SJ, Younoszai MK and Thomas LN, 1966. Influence of vitamin D on linear growth of normal full-term infants. Journal of Nutrition, 88, 345-350.

Ford ES, Zhao G, Tsai J and Li C, 2011. Vitamin D and all-cause mortality among adults in USA: findings from the National Health and Nutrition Examination Survey Linked Mortality Study. International Journal of Epidemiology, 40, 998-1005.

Freedman DM, Looker AC, Abnet CC, Linet MS and Graubard BI, 2010. Serum 25-hydroxyvitamin D and cancer mortality in the NHANES III study (1988-2006). Cancer Research, 70, 8587-8597.

Gallagher JC, Sai A, Templin T, 2nd and Smith L, 2012. Dose response to vitamin D supplementation in postmenopausal women: a randomized trial. Annals of Internal Medicine, 156, 425-437.

Ginde AA, Scragg R, Schwartz RS and Camargo CA, Jr., 2009. Prospective study of serum 25-hydroxyvitamin D level, cardiovascular disease mortality, and all-cause mortality in older U.S. adults. Journal of the American Geriatrics Society, 57, 1595-1603.

Gordon CM, Williams AL, Feldman HA, May J, Sinclair L, Vasquez A and Cox JE, 2008. Treatment of hypovitaminosis D in infants and toddlers. Journal of Clinical Endocrinology and Metabolism, 93, 2716-2721.

Grandi NC, Breitling LP and Brenner H, 2010. Vitamin D and cardiovascular disease: systematic review and meta-analysis of prospective studies. Preventive Medicine, 51, 228-233.

Grimnes G, Joakimsen R, Figenschau Y, Torjesen PA, Almas B and Jorde R, 2012. The effect of high-dose vitamin D on bone mineral density and bone turnover markers in postmenopausal women with low bone mass--a randomized controlled 1-year trial. Osteoporosis International, 23, 201-211.

Haddad JG and Chyu KJ, 1971. Competitive protein-binding radioassay for 25-hydroxycholecalciferol. Journal of Clinical Endocrinology and Metabolism, 33, 992-995.

Haddock L, Corcino J and Vazquez MC, 1982. 25(OH)D serum levels in the normal Puerto Rican population and in subjects with tropical sprue and parathyroid disease. Puerto Rico Health Sciences Journal, 1, 85-91.

Hasling C, Nielsen HE, Melsen F and Mosekilde L, 1987. Safety of osteoporosis treatment with sodium fluoride, calcium phosphate and vitamin D. Mineral and Electrolyte Metabolism, 13, 96-103.

Hathcock JN, Shao A, Vieth R and Heaney R, 2007. Risk assessment for vitamin D. American Journal of Clinical Nutrition, 85, 6-18.

Heaney RP, Davies KM, Chen TC, Holick MF and Barger-Lux MJ, 2003. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. American Journal of Clinical Nutrition, 77, 204-210.

Hintzpeter B, Mensink GB, Thierfelder W, Muller MJ and Scheidt-Nave C, 2008. Vitamin D status and health correlates among German adults. European Journal of Clinical Nutrition, 62, 1079-1089.

Holick MF, 2006. Vitamin D. In: Modern Nutrition in Health and Disease. Eds Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ. Lippincott Williams & Wilkins, Philadelphia, 376-395 pp.

Hollis BW and Wagner CL, 2004. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. American Journal of Clinical Nutrition, 80, 1752S-1758S.

Hollis BW, Johnson D, Hulsey TC, Ebeling M and Wagner CL, 2011. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. Journal of Bone and Mineral Research, 26, 2341-2357.

Hutchinson MS, Grimnes G, Joakimsen RM, Figenschau Y and Jorde R, 2010. Low serum 25-hydroxyvitamin D levels are associated with increased all-cause mortality risk in a general population: the Tromso study. European Journal of Endocrinology, 162, 935-942.

Hyppönen E, Fararouei M, Sovio U, Hartikainen AL, Pouta A, Robertson C, Whittaker JC and Jarvelin MR, 2011. High-dose vitamin D supplements are not associated with linear growth in a large Finnish cohort. Journal of Nutrition, 141, 843-848.

IoM (Institute of Medicine), 1997. Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. National Academy Press, Washington D.C., USA, 454 pp.

IoM (Institute of Medicine), 2010. Dietary Reference Intakes for calcium and vitamin D. National Academies Press, Washington, D.C., USA, 1133 pp.

Ish-Shalom S, Segal E, Salganik T, Raz B, Bromberg IL and Vieth R, 2008. Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients. Journal of Clinical Endocrinology and Metabolism, 93, 3430-3435.

IUNA (Irish Universities Nutrition Alliance), 2011. National Adult Nutrition Survey.

IUNA (Irish Universities Nutrition Alliance), a. National Children's Food Survey 2003-2004. Available from: http://www.iuna.net. Accessed on June 2012.

IUNA (Irish Universities Nutrition Alliance), b. The National Teens' Food Survey 2005-2006. Available from: http://www.iuna.net/. Accessed on June 2012.

Jacobus CH, Holick MF, Shao Q, Chen TC, Holm IA, Kolodny JM, Fuleihan GE and Seely EW, 1992. Hypervitaminosis D associated with drinking milk. New England Journal of Medicine, 326, 1173-1177.

Jassal SK, Chonchol M, von Muhlen D, Smits G and Barrett-Connor E, 2010. Vitamin D, parathyroid hormone, and cardiovascular mortality in older adults: the Rancho Bernardo study. American Journal of Medicine, 123, 1114-1120.

Jeans PC and Stearns G, 1938. The effect of vitamin D on linear growth in infancy: II. The effect of intakes above 1,800 U.S.P. units daily. The Journal of Pediatrics, 13, 730-740.

Jia X, Aucott LS and McNeill G, 2007. Nutritional status and subsequent all-cause mortality in men and women aged 75 years or over living in the community. British Journal of Nutrition, 98, 593-599.

Johansson H, Oden A, Kanis J, McCloskey E, Lorentzon M, Ljunggren O, Karlsson MK, Thorsby PM, Tivesten A, Barrett-Connor E, Ohlsson C and Mellstrom D, 2011. Low serum vitamin D is associated with increased mortality in elderly men: MrOS Sweden. Osteoporosis International, 23, 991-999.

Johansson LR, Solvoll K, Bjorneboe GE and Drevon CA, 1998. Intake of very-long-chain n-3 fatty acids related to social status and lifestyle. European Journal of Clinical Nutrition, 52, 716-721.

Jones G, 2008. Pharmacokinetics of vitamin D toxicity. American Journal of Clinical Nutrition, 88, 582S-586S.

Jones G, Prosser DE and Kaufmann M, 2012. 25-Hydroxyvitamin D-24-hydroxylase (CYP24A1): Its important role in the degradation of vitamin D. Archives of Biochemistry and Biophysics, 523, 9-18.

Jorde R, Sneve M, Torjesen P and Figenschau Y, 2010. No improvement in cardiovascular risk factors in overweight and obese subjects after supplementation with vitamin D3 for 1 year. Journal of Internal Medicine, 267, 462-472.

Kauppi M, Impivaara O, Maki J, Heliovaara M, Marniemi J, Montonen J and Jula A, 2009. Vitamin D status and common risk factors for bone fragility as determinants of quantitative ultrasound variables in a nationally representative population sample. Bone, 45, 119-124.

Kyttälä P, Ovaskainen M, Kronberg-Kippilä C, Erkkola M, Tapanainen H, Tuokkola J, Veijola R, Simell O, Knip M and Virtanen SM, 2008. The Diet of Finnish Preschoolers. B32/2008, National Public Health Institute, 158 pp.

Kyttälä P, Erkkola M, Kronberg-Kippila C, Tapanainen H, Veijola R, Simell O, Knip M and Virtanen SM, 2010. Food consumption and nutrient intake in Finnish 1-6-year-old children. Public Health Nutrition, 13, 947-956.

Lappe JM, Travers-Gustafson D, Davies KM, Recker RR and Heaney RP, 2007. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. American Journal of Clinical Nutrition, 85, 1586-1591.

Lopes C, Oliveira A, Santos AC, Ramos E, Gaio AR, Severo M and Barros H, 2006. Consumo alimentar no Porto. Faculdade de Medecina da Universidade do Porto, 172 pp.

Lowe H, Cusano NE, Binkley N, Blaner WS and Bilezikian JP, 2011. Vitamin D toxicity due to a commonly available "over the counter" remedy from the Dominican Republic. Journal of Clinical Endocrinology and Metabolism, 96, 291-295.

Maalouf J, Nabulsi M, Vieth R, Kimball S, El-Rassi R, Mahfoud Z and El-Hajj Fuleihan G, 2008. Short- and long-term safety of weekly high-dose vitamin D3 supplementation in school children. Journal of Clinical Endocrinology and Metabolism, 93, 2693-2701.

Macdonald HM, Mavroeidi A, Barr RJ, Black AJ, Fraser WD and Reid DM, 2008. Vitamin D status in postmenopausal women living at higher latitudes in the UK in relation to bone health, overweight, sunlight exposure and dietary vitamin D. Bone, 42, 996-1003.

Manios Y, Grammatikaki E, Papoutsou S, Liarigkovinos T, Kondaki K and Moschonis G, 2008. Nutrient intakes of toddlers and preschoolers in Greece: the GENESIS study. Journal of the American Dietetic Association, 108, 357-361.

Melamed ML, Michos ED, Post W and Astor B, 2008. 25-hydroxyvitamin D levels and the risk of mortality in the general population. Archives of Internal Medicine, 168, 1629-1637.

Michaelsson K, Baron JA, Snellman G, Gedeborg R, Byberg L, Sundstrom J, Berglund L, Arnlov J, Hellman P, Blomhoff R, Wolk A, Garmo H, Holmberg L and Melhus H, 2010. Plasma vitamin D and mortality in older men: a community-based prospective cohort study. American Journal of Clinical Nutrition, 92, 841-848.

Mocanu V, Stitt PA, Costan AR, Voroniuc O, Zbranca E, Luca V and Vieth R, 2009. Long-term effects of giving nursing home residents bread fortified with 125 microg (5000 IU) vitamin D(3) per daily serving. American Journal of Clinical Nutrition, 89, 1132-1137.

MRI, 2008. National Verzehrs Studie II. Ergebnisbericht, Teil 2. Die bundesweite Befragung zur Ernährung von Jugendlichen und Erwachsenen. Max Rubner-Institut Bundesforschungsinstitut für Ernährung und Lebensmittel, 307 pp.

Narang NK, Gupta RC and Jain MK, 1984. Role of vitamin D in pulmonary tuberculosis. Journal of the Association of Physicians of India, 32, 185-188.

Ocke MC, van Rossum CTM, Fransen HP, Buurma EJM, de Boer EJ, Brants HAM, Niekerk EM, van der Laan JD, Drijvers JJMM and Ghameshlou Z, 2008. Dutch National Food Consumption Survey - Young Children 2005/2006. RIVM Report 350070001/2008, National Institute for Public Health and the Environment, 105 pp.

Paturi M, Tapanainen H, Reinivuo H and Pietinen P, 2008. The National FINDiet 2007 Survey. Report B23/2008, KTL-National Public Health Institute, 230 pp.

Pedersen AN, Fagt S, Groth MV, Christensen T, Biltoft-Jensen A, Matthiessen J, Lyhne Andersen N, Kørup K, Hartkopp H, Hess Ygil K, Hinsch HJ, Saxholt E and Trolle E, 2010. Danskernes kostvaner 2003-2008. Hovedresultater [Dietary habits in Denmark 2003-2008. Main results]. DTU Fødevareinstituttet, 200 pp.

Pettifor JM, Bikle DD, Cavaleros M, Zachen D, Kamdar MC and Ross FP, 1995. Serum levels of free 1,25-dihydroxyvitamin D in vitamin D toxicity. Annals of Internal Medicine, 122, 511-513.

Rickers H, Deding A, Christiansen C, Rodbro P and Naestoft J, 1982. Corticosteroid-induced osteopenia and vitamin D metabolism. Effect of vitamin D2, calcium phosphate and sodium fluoride administration. Clinical Endocrinology, 16, 409-415.

Rizzoli R, Stoermann C, Ammann P and Bonjour JP, 1994. Hypercalcemia and hyperosteolysis in vitamin D intoxication: effects of clodronate therapy. Bone, 15, 193-198.

SCF (Scientific Committee on Food), 2003. Opinion on the Tolerable Upper Intake Level of vitamin D. 35 pp.

Schwartzman MS and Franck WA, 1987. Vitamin D toxicity complicating the treatment of senile, postmenopausal, and glucocorticoid-induced osteoporosis. Four case reports and a critical commentary on the use of vitamin D in these disorders. American Journal of Medicine, 82, 224-230.

Seamans KM and Cashman KD, 2009. Existing and potentially novel functional markers of vitamin D status: a systematic review. American Journal of Clinical Nutrition, 89, 1997S-2008S.

Selby PL, Davies M, Marks JS and Mawer EB, 1995. Vitamin D intoxication causes hypercalcaemia by increased bone resorption which responds to pamidronate. Clinical Endocrinology, 43, 531-536.

Semba RD, Houston DK, Ferrucci L, Cappola AR, Sun K, Guralnik JM and Fried LP, 2009. Low serum 25-hydroxyvitamin D concentrations are associated with greater all-cause mortality in older community-dwelling women. Nutrition Research, 29, 525-530.

Semba RD, Houston DK, Bandinelli S, Sun K, Cherubini A, Cappola AR, Guralnik JM and Ferrucci L, 2010. Relationship of 25-hydroxyvitamin D with all-cause and cardiovascular disease mortality in older community-dwelling adults. European Journal of Clinical Nutrition, 64, 203-209.

Sette S, Le Donne C, Piccinelli R, Arcella D, Turrini A and Leclercq C, 2010. The third Italian National Food Consumption Survey, INRAN-SCAI 2005-06 - Part 1: Nutrient intakes in Italy. Nutrition, Metabolism and Cardiovascular Diseases, 1-11.

Sioen I, Matthys C, De Backer G, Van Camp J and Henauw SD, 2007b. Importance of seafood as nutrient source in the diet of Belgian adolescents. Journal of Human Nutrition and Dietetics, 20, 580-589.

Skinner HG, Michaud DS, Giovannucci E, Willett WC, Colditz GA and Fuchs CS, 2006. Vitamin D intake and the risk for pancreatic cancer in two cohort studies. Cancer Epidemiology, Biomarkers and Prevention, 15, 1688-1695.

Sneve M, Figenschau Y and Jorde R, 2008. Supplementation with cholecalciferol does not result in weight reduction in overweight and obese subjects. European Journal of Endocrinology, 159, 675-684.

Snijder MB, van Dam RM, Visser M, Deeg DJ, Dekker JM, Bouter LM, Seidell JC and Lips P, 2005. Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. Journal of Clinical Endocrinology and Metabolism, 90, 4119-4123.

Specker BL, Tsang RC and Hollis BW, 1985. Effect of race and diet on human-milk vitamin D and 25-hydroxyvitamin D. American Journal of Diseases of Children, 139, 1134-1137.

Stolzenberg-Solomon RZ, Jacobs EJ, Arslan AA, Qi D, Patel AV, Helzlsouer KJ, Weinstein SJ, McCullough ML, Purdue MP, Shu XO, Snyder K, Virtamo J, Wilkins LR, Yu K, Zeleniuch-Jacquotte A, Zheng W, Albanes D, Cai Q, Harvey C, Hayes R, Clipp S, Horst RL, Irish L, Koenig K, Le Marchand L and Kolonel LN, 2010. Circulating 25-hydroxyvitamin D and risk of pancreatic cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. American Journal of Epidemiology, 172, 81-93.

Tetens I, Biltoft-Jensen A, Spagner C, Christensen T, Gille MB, Bugel S and Banke Rasmussen L, 2011. Intake of micronutrients among Danish adult users and non-users of dietary supplements. Food and Nutrition Research, 55, 7153-7161.

Tjellesen L, Hummer L, Christiansen C and Rodbro P, 1986. Serum concentration of vitamin D metabolites during treatment with vitamin D2 and D3 in normal premenopausal women. Bone and Mineral, 1, 407-413.

Tripkovic L, Lambert H, Hart K, Smith CP, Bucca G, Penson S, Chope G, Hyppönen E, Berry J, Vieth R and Lanham-New S, 2012. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. American Journal of Clinical Nutrition, ahead of print.

Tsiaras WG and Weinstock MA, 2011. Factors influencing vitamin D status. Acta Dermato-Venereologica, 91, 115-124.

van Rossum CTM, Fransen HP, Verkaik-Kloosterman J, Buurma-Rethans EJM and Ocké MC, 2011. Dutch National Food Consumption Survey 2007-2010: Diet of children and adults aged 7 to 69 years. RIVM Report number: 350050006/2011, National Institute for Public Health and the Environment, 148 pp.

Vervel C, Zeghoud F, Boutignon H, Tjani JC, Walrant-Debray O and Garabedian M, 1997. [Fortified milk and supplements of oral vitamin D. Comparison of the effect of two doses of vitamin D (500 and 1,000 UI/d) during the first trimester of life]. Archives de Pediatrie, 4, 126-132.

Vieth R, 1990. The mechanisms of vitamin D toxicity. Bone and Mineral, 11, 267-272.

Vieth R, 1999. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. American Journal of Clinical Nutrition, 69, 842-856.

Vieth R, Chan PC and MacFarlane GD, 2001. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. American Journal of Clinical Nutrition, 73, 288-294.

Virtanen JK, Nurmi T, Voutilainen S, Mursu J and Tuomainen TP, 2011. Association of serum 25-hydroxyvitamin D with the risk of death in a general older population in Finland. European Journal of Nutrition, 50, 305-312.

Visser M, Deeg DJ, Puts MT, Seidell JC and Lips P, 2006. Low serum concentrations of 25-hydroxyvitamin D in older persons and the risk of nursing home admission. American Journal of Clinical Nutrition, 84, 616-622.

Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, Margolis KL, Ockene JK, Phillips L, Pottern L, Prentice RL, Robbins J, Rohan TE, Sarto GE, Sharma S, Stefanick ML, Van Horn L, Wallace RB, Whitlock E, Bassford T, Beresford SA, Black HR, Bonds DE, Brzyski RG, Caan B, Chlebowski RT, Cochrane B, Garland C, Gass M, Hays J, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Jackson RD, Johnson KC, Judd H, Kooperberg CL, Kuller LH, LaCroix AZ, Lane DS, Langer RD, Lasser NL, Lewis CE, Limacher MC and Manson JE, 2006. Calcium plus vitamin D supplementation and the risk of colorectal cancer. New England Journal of Medicine, 354, 684-696.

Wagner D, Hanwell HE, Schnabl K, Yazdanpanah M, Kimball S, Fu L, Sidhom G, Rousseau D, Cole DE and Vieth R, 2011. The ratio of serum 24,25-dihydroxyvitamin D(3) to 25-hydroxyvitamin D(3) is predictive of 25-hydroxyvitamin D(3) response to vitamin D(3) supplementation. Journal of Steroid Biochemistry and Molecular Biology, 126, 72-77.

Wallace RB, Wactawski-Wende J, O'Sullivan MJ, Larson JC, Cochrane B, Gass M and Masaki K, 2011. Urinary tract stone occurrence in the Women's Health Initiative (WHI) randomized clinical trial of calcium and vitamin D supplements. American Journal of Clinical Nutrition, 94, 270-277.

Webb AR, DeCosta BR and Holick MF, 1989. Sunlight regulates the cutaneous production of vitamin D3 by causing its photodegradation. Journal of Clinical Endocrinology and Metabolism, 68, 882-887.

Zittermann A, Frisch S, Berthold HK, Gotting C, Kuhn J, Kleesiek K, Stehle P, Koertke H and Koerfer R, 2009. Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. American Journal of Clinical Nutrition, 89, 1321-1327.

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	
					65	65	74		7.1			12.1	
		The Netherlands	(van Rossum et al., 2011)	Two non-consecutive 24-hour dietary recalls	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	
		United Kingdom	(Bates et al., 2011)	4-day record	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			10.0	
					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**	(Kyttälä 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**	(Kyttälä 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 supple-ment	Effect Intervention group with highest dose		Effect Control group		Hyper-calcaemia	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 Bad Oeynhausen, Germany (latitude 52°N)	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	
Narang et al., 1984 Ajmer, India (latitude 26°N)	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	

Author	Study Design	Duration	Number at entry and type of subjects	Age range	Sex	Completers	Vitamin D supplement	Ca supple-ment	Effect Intervention group with highest dose		Effect Control group		Hyper-calcaemia	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 Long Island in NY, USA (latitude 40°N)	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 D₃ 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 D₃/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 Toronto, Canada (latitude 43°N)	Rando-mised	5 (starting between January and February)	73 healthy adults	18-56	both	61 completed ≥1 month	25 or 100 µg/day D₃	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 D₃, hypercalciuria occurred in 2 of 6 measure-ments, but time points not specified.

Author	Study Design	Duration	Number at entry and type of subjects	Age range	Sex	Completers	Vitamin D supplement	Ca supple-ment	Effect Intervention group with highest dose		Effect Control group		Hyper-calcaemia	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 Copenhagen, Denmark (latitude 55°N)	Rando-mised, double-blind uncon-trolled	8 weeks (September-November)	19 healthy premeno-pausal 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 Omaha, Nebraska (latitude 41°N)	Rando-mised, placebo-controlled	12 (screening in 2 successive years in April or January to May, enroll-ment on average 5 weeks after screening)	163 healthy postmeno-pausal 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 supple-ment	Effect Intervention group with highest dose		Effect Control group		Hyper-calcaemia	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)	Uncon-trolled	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) Tromso, Norway (latitude 69°N)	Rando-mised, double-blind, placebo-controlled	12 (starting November)	438 over-weight 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 supple-ment	Effect Intervention group with highest dose		Effect Control group		Hyper-calcaemia	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 Tromso, Norway (latitude 69°N)	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 September 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±0.10 163 µg/day D$_3$: t$_0$: 2.36±0.09 Δ: 0.02±0.09	20 µg/day D$_3$: t$_0$: 71.2±22.3 Δ: +18.0±18.9 163 µg/day D$_3$: t$_0$: 70.7±23.0 Δ: +114.7±34.6	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 Björkhem I, 1987) Stockholm, Sweden (latitude 59°N)	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 Omaha, USA (latitude 41°N)	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		Hyper-calcaemia	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 Glostrup, Denmark (latitude 54°N)	Rando-mised, 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)D_2** t_0: 4.2±1.2 t_{24}: 145.3±19.0 **25(OH)D_3** 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)D_2** t_0: 8.7±2.2 t_{24}: 7.2±3.5 **25(OH)D_3** t_0: 42.7±5.5 t_{24}: 34.4 ±5.5 (mean±SEM)	Not reported	
Hasling et al., 1987 Aarhus, Denmark (latitude 56°N)	Uncon-trolled	5 years (mean observation time 2.8 years)	163 consecutive patients with spinal crush fracture osteopo-rosis	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 Omaha, USA (latitude 41°N)	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 supple-ment	Effect Intervention group with highest dose		Effect Control group		Hyper-calcaemia	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 New York, USA (latitude 42°N)	Case reports	6 weeks – 5 years	4 patients with osteoporo-sis (3) or osteomala-cia (1); 2 of 4 with corticoid therapy; 1 with renal insufficien-cy	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 Manchester, UK (latitude 53°N)	Case reports	10 years	6 patients with hypopara-thyroidism, hypophos-phataemic rickets, coelic disease, paraesthe-siae 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 supple-ment	Effect Intervention group with highest dose		Effect Control group		Hyper-calcaemia	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 hypopara-thyroidism, Paget's disease, arthritis, vit. D-resistant rickets, osteopo-rosis, or symptoms suggesting carpal-tunnel syndrome	59	both	n/a	1,250-2,500 µg D₂/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 D₂/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 osteoporo-sis, or hypopara-thyroidism	72	both	n/a	2,143 µg/day D₃	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 D₃		2.83	801				
		74 weeks		50			7,500 µg/day D₃		3.30	1,692				
		12 weeks		66			1,071 µg/day D₃		2.53	374				
		4 weeks		84			7,500 µg/day D₃		4.59	650				
		4 weeks		79			7,500 µg/day D₃		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)
$1,25(OH)_2D$	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