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Evaluation of tolerable upper intake levels for vitamin D in children and adolescents

Statement of the Norwegian Scientific Committee for Food Safety

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Evaluation of tolerable upper intake levels for vitamin D in children and adolescents

The Statement has been prepared by members of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy

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Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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Summary

In 2012, the European Food Safety Authority (EFSA) suggested a tolerable upper intake level (UL) for vitamin D at 100 µg/day for adults based on the risk of hypercalcaemia. EFSA concluded that consumption of up to 50 µg/day does not lead to hypercalcaemia in children and adolescents (10-17 years). Furthermore, EFSA stated that there is no reason to assume that children and 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 and 50 µg/day in children 1-10 years, taking the smaller body size into account, was proposed.

The Norwegian Food Safety Authority (NFSA) is currently revising the national regulation of maximum limits in food supplements (not yet harmonised in the European Economic Area (EEA)), including maximum limits for vitamin D. NFSA has therefore requested the Norwegian Scientific Committee for Food Safety (VKM) to evaluate the assumption in the EFSA opinion that children and adolescents can tolerate the same amount of vitamin D as adults due to rapid bone formation and growth. In children and adolescents with lower weight than adults, this assumption actually implies that adolescents can tolerate more vitamin D per kg body weight than adults. VKM is therefore requested to evaluate if there is scientific evidence that a UL at 50 µg/day for children (1-10 years) and 100 µg/day for adolescents (11-17 years) is safe.

The present statement is prepared by members of the Panel on Nutrition, Dietetic Products and Novel Food and Allergy in VKM.

Three literature searches were performed to find new relevant studies investigating high intakes of vitamin D in children and adolescents and the role of vitamin D in bone formation and growth.

No studies supporting a higher tolerance to vitamin D in children and adolescents due to rapid bone formation and growth were retrieved in the literature search. Moreover, there is apparently no firm association between bone formation and vitamin D levels in children during their growth period into adolescence and adulthood.

No studies investigating high intakes of vitamin D in children 1-10 years were found. Furthermore, no studies that have examined safety issues and/or adverse effects of vitamin D supplementation in doses above 50 µg/day in adolescents were identified. It can therefore not be concluded that the UL at 50 µg/day in children (1-10 years) and 100 µg/day in adolescents (11-17 years) is safe.

In the 2002 report from European Scientific Committee on Food (SCF), a UL was set at 25 µg/day for children aged 2-10 years, and 50 µg/day for adolescents aged 11-17 years (corresponding to the UL for adults at that time). To the best of knowledge no serious, harmful effects have been reported for these doses of vitamin D.

Key words: VKM, Norwegian Scientific Committee for Food Safety, tolerable upper intake level, UL, vitamin D, children, adolescents.

Sammendrag på norsk

I 2012 fastsatte EUs mattrygghetsorgan European Food Safety Authority (EFSA) et tolerabelt øvre inntaksnivå (UL) for vitamin D på 100 µg/dag for voksne basert på risikoen for hyperkalsemi. EFSA konkluderte med at et inntak opp til 50 µg/dag ikke fører til hyperkalsemi hos barn og ungdom (10-17 år). Videre uttalte EFSA at det ikke er grunn til å anta at barn og unge i beindannelsesfase og rask vekst har en lavere toleranse for vitamin D enn voksne, og foreslo derfor en UL på 100 µg/dag for ungdom i alderen 11-17 år og 50 µg/dag for barn 1-10 år, tatt i betraktning mindre kroppsstørrelse i de lavere aldersgruppene.

Mattilsynet er i ferd med å revidere forskrift om kosttilskudd med nasjonale maksimumsgrenser (foreløpig ikke er harmonisert i EØS-området), herunder maksimumsgrenser for vitamin D. I forbindelse med dette arbeidet har Mattilsynet bedt Vitenskapskomiteen for mattrygghet (VKM) å vurdere forutsetningen EFSA har lagt til grunn om at barn og unge kan tolerere den samme mengden vitamin D som voksne på grunn av rask beindannelse og vekst. For barn og unge med lavere kroppsvekt enn voksne, innebærer denne antakelsen at de skal tolerere mer vitamin D per kg kroppsvekt enn voksne. VKM er derfor bedt om å vurdere om det finnes vitenskapelig dokumentasjon for at en UL på 50 µg/dag for barn (1-10 år) og 100 µg/dag for ungdom (11-17 år) er trygt.

Denne vurderingen er utarbeidet av medlemmer i Faggruppen for ernæring, dietetiske produkter, ny mat og allergi i VKM.

Tre litteratursøk ble utført for å finne nye relevante studier som har undersøkt høyt inntak av vitamin D hos barn og ungdom, samt vitamin D metabolismen under beindannelse og vekst.

Det ble ikke funnet studier som viser at barn og ungdom har en høyere toleranse for vitamin D på grunn av rask beindannelse og vekst. Studiene viser ingen konsistent sammenheng mellom beindannelse og vitamin D-nivåer hos barn og ungdom i vekst.

Det ble ikke funnet noen studier som har undersøkt høyt inntak av vitamin D hos barn i alderen 1-10 år. Det ble heller ikke avdekket studier som har undersøkt sikkerhet og/eller bivirkninger fra vitamin D-tilskudd i doser over 50 µg/dag hos ungdom. Det kan derfor ikke konkluderes med at UL på 50 µg/dag hos barn (1-10 år) og 100 µg/dag hos ungdom (11-17 år) er trygt.

I rapporten fra EUs tidligere mattrygghetsorgan, Scientific Committee for Food (SCF) fra 2002, ble UL satt til 25 µg/dag for barn i alderen 2-10 år, og 50 µg/dag for ungdom i alderen 11-17 år (tilsvarende den daværende UL for voksne). Ut fra hva vi har kunnet se i tilgjengelig litteratur er det ikke rapportert om alvorlige, skadelige effekter med disse dosene av vitamin D til barn, respektive ungdom.

Abbreviations and conversion factors

BMC: Bone mineral content
BMD: Bone mineral density
DXA: Dual-energy X-ray absorptiometry
NOAEL: No observed adverse effect level
PTH: Parathyroid hormone
RCT: Randomised controlled trial

1 IU vitamin D = 0.025 µg vitamin D
1 ng/mL 25-(OH)-vitamin D = 2.496 nmol/L 25-(OH)-vitamin D
1 mg/dL serum calcium = 0.25 mmol/L serum calcium

Background as provided by the Norwegian Food Safety Authority

In January 2013, the Panel on Nutrition, Dietetic Products, Novel Food and Allergy in the Norwegian Scientific Committee for Food Safety (VKM) published the opinion "Assessment of vitamin A and D in food supplements." In the VKM opinion, reference is made to the European Food Safety Authority (EFSA) opinion on tolerable upper intake level (UL) for vitamin D.

In 2012, EFSA suggested a UL for vitamin D at 100 µg/day for adults based on the risk of hypercalcaemia. EFSA stated in their opinion that only two new studies investigating high doses of vitamin D supplementation in children and adolescents 10-17 years had been conducted since the previous opinion on vitamin D was published from the Scientific Committee on Food (SCF) in 2002. EFSA concluded that consumption of up to 50 µg/day does not lead to hypercalcaemia in children and adolescents (10-17 years). EFSA stated that while there are no studies at higher intakes, there is no reason to assume that adolescents in the phase of rapid bone formation and growth have a lower tolerance for vitamin D compared to adults. Thus, a UL of 100 µg/day for adolescents aged 11-17 years was proposed.

For children 1-10 years, no new data were found after the SCF assessment in 2002. EFSA considered that there is no reason to assume that children in the phase of rapid bone formation and growth have a lower tolerance for vitamin D compared to adults, and suggested a UL of 50 µg/day, taking the smaller body size into account.

The SCF stated in 2002 that no studies had investigated intake of high levels of vitamin D in the age group 2-17 years. They further stated that the sensitivity to vitamin D seemed to change with age. Using a conservative approach where a lower body weight in children up to 10 years was considered, the SCF set a UL at 25 µg/day for children aged 2-10 years, and 50 µg/day for adolescents aged 11-17 years (corresponding to the UL for adults at that time).

In the new Nordic Nutrition Recommendations (NNR5) from 2012, UL and toxicity from vitamin D intake are only briefly discussed, and reference is made to the EFSA UL from 2012 for children and adolescents (NNR, 2012).

In 2000, SCF published guidelines for development of tolerable upper intake levels for vitamins and minerals in children and adolescents, using reference body weights (SCF, 2000). This approach is based on the assumption that children metabolise vitamins and minerals similar to adults per kg body weight. However, in the UL for vitamin D from EFSA this weight scaling based approach has not been considered. Consequently, it is assumed that children and adolescents tolerate a higher daily intake of vitamin D per kg body weight than adults. The scientific basis for this assumption is not provided in the opinion.

The national maximum limit for vitamin D in food supplements are currently 10 µg per recommended daily dose. In 2013, at the request of the Norwegian Food Safety Authority, VKM conducted a risk assessment of the national maximum limits for vitamin A and D. Based on the updated UL from EFSA and new recommendations from NNR for elderly (increased to 20 µg/day), VKM suggested that the national maximum limits could be increased to 20 µg

per recommended daily dosage for children (above 3 years) and adults. Previous to establishment of the new national maximum limits, the Norwegian Food Safety Authority therefore requests an evaluation of the UL for children and adolescents.

Terms of reference

In the EFSA opinion on the tolerable upper intake level (UL) of vitamin D from 2012, UL for vitamin D is set at 100 µg/day for adults and adolescents aged 11-17 years, and 50 µg/day for children aged 1-10 years, taking into account the smaller body size in the younger age groups.

EFSA considered that there is no reason to believe that children and adolescents in the phase of rapid bone formation and growth have a lower tolerance for vitamin D compared to adults. In children and adolescents with lower weight than adults this assumption actually implies that they must tolerate more vitamin D per kg body weight than adults.

The Norwegian Food Safety Authority requests the Norwegian Scientific Committee for Food Safety (VKM) to evaluate this assumption in the EFSA opinion. VKM is therefore requested to evaluate if there is scientific evidence that a UL at 50 µg/day for children (1-10 years) and 100 µg/day for adolescents (11-17 years) is safe.

The Norwegian Food Safety Authority requests VKM to answer the following questions:

1. What is the scientific evidence for the assumption in the EFSA opinion?
2. Is there scientific evidence that a UL at 50 µg/day for children (1-10 years) and 100 µg/day for adolescents (11-17 years) is safe?

1 Introduction

To answer the terms of reference, the project group has endeavored to identify any scientific reports or published studies relevant for high intakes of vitamin D in children above one year and adolescents. The reports on tolerable upper intake levels of vitamin D from the Scientific Committee on Food (2002), European Food Safety Authority (EFSA) (2012), Institute of Medicine (1997 and 2011) and the Nordic Nutrition Recommendations (NNR5) (2012) were assessed, and literature searches performed to retrieve relevant scientific publications.

2 Reports on UL for vitamin D

2.1 SCF, 2002 and EFSA, 2012

The Scientific Committee for Food (SCF) arrived in 2002 at a UL of 50 μg/day for adults. This was particularly based on two studies that reported adverse effects at intake levels exceeding 100 μg/day, and included a safety margin-factor of 2 (SCF, 2002). The SCF also wrote (page 15, top): "Further studies are needed to clarify progressive health effects of regular and moderately high amounts of vitamin D over several decades." Notably the UL for adults were increased to 100 μg/day in the EFSA 2012 based on data from two recent studies in adult men (EFSA, 2012).

For infants, the SCF cautioned in 2002 that most data were derived from old studies and case reports. Moreover, the SCF wrote (page 22, top paragraph): "However, based on these data, it cannot be excluded that an increased risk of vitamin D toxicity and hypercalcaemia might be present at exposures below 50 μg/day." SCF set UL for 0-10 year old children at 25 μg/day, and 50 μg/day for those between 11 and 17 years. In the 2012 opinion, EFSA set the UL for children aged 1-10 years at 50 μg/day and for children aged 11-17 at 100 μg/day (EFSA, 2012). The reason for the increase was two new reports failing to identify hypercalcaemia at an intake of 50 μg/day in adolescents (El-Hajj Fuleihan et al., 2006; Maalouf et al., 2008). The updated UL was derived from a no observed effect level (NOAEL) set at 250 μg/day on the basis of the two studies in adult men, and then applying a safety margin of 2.5 to address the uncertainties underlying the NOAEL.

No studies were cited to support the assumption that children or adolescents could tolerate the same amount of vitamin D as adults because of growth and rapid bone formation.

Concluding remark: There are no studies included in the EFSA (or SCF) opinion to support the assumption that adolescents (11-17 years) can tolerate the same amount of vitamin D as adults due to rapid bone formation and growth.

There are no studies included in the EFSA (or SCF) opinion that have investigated use of dosages above 25 μg/day vitamin D in children (1-10 years), and no studies that have investigated dosages above 50 μg/day in adolescents.

2.2 Institute of Medicine (IOM), 1997 and 2111

In the section concerning ULs for children and adolescents 1 through 18 years of age (page 445), the Institute of Medicine (IOM) states that no specific data are available for age groups other than adults and infants (IOM, 2011). In 1997 it was decided that increased rates of bone formation in toddlers, children, and adolescents suggested that the adult UL is appropriate for these age groups (IOM, 1997). In the 2011 edition, the UL for younger children is 2,500 IU/day (63 μg/day) for 1-3 year olds and 3,000 IU/day (75 μg/day) for 4-8 year olds. This represents a down-scaling of the adult UL, in order to be more consistent with concepts of graded tolerances with maturity. The simulated dose-response relationship between vitamin D intake and serum 25-(OH)-vitamin D level was not affected by age. The data available did not include any children younger than six years old. According to the IOM, there is no quantitative basis for such scaling, but it reflects a cautious and prudent

approach given current biological understandings. Children and adolescents 9-18 years of age have UL at 100 μg/day, the same as that for adults.

Concluding remark: The IOM report did not provide further information on tolerance to or safety of high-dosage vitamin D in children and adolescents.

3 Literature search

3.1 Search strategy

Two literature searches were performed to retrieve publications addressing high intakes of vitamin D in children and adolescents; one retrieving systematic reviews and meta-analyses, and the second retrieving randomised controlled trials. The strategy for the literature searches was discussed and accepted in the project group and conducted by the secretariat.

The first literature search for systematic reviews and meta-analyses was conducted in Medline using a combination of both controlled vocabulary and text words including the following search criteria: vitamin D AND child OR adolescent.

The literature search was limited by including only systematic reviews or meta-analyses with human studies in the age group 0-18 years, and by limiting the languages to Danish, English, Norwegian and Swedish. Publication year was limited to the period 1980 to 2014.

The second literature search for randomised, controlled trials was conducted in PubMed including the following criteria: high dose* OR high intake OR toxic* OR risk OR safe* OR upper level* AND vitamin D.

The literature search was limited by including only human studies filtered as randomised, controlled trials in the age group 0-18 years, and by limiting the languages to Danish, English, Norwegian and Swedish. Publication year was limited to 10 years back in time to retrieve relatively new studies.

These two literature searches were performed on the 4th of April 2014.

A third literature search was performed to identify studies investigating the role of vitamin D in bone formation and growth in children and adolescents. The search was conducted in Medline using a combination of both controlled vocabulary and text words including the following search criteria: vitamin D AND bone* OR calcification OR bone density/or bone mineralisation OR bone turnover* OR bone metabolism*. The literature search was limited by including only human studies filtered as randomised, controlled trials or systematic reviews or meta-analyses in the age groups preschool child (2-5 years), child (6-12 years), or adolescent (13-18 years). The languages were limited to Danish, English, Norwegian and Swedish, and the search period was limited to the period 1980 to 2014. This search was performed on the 12th of May 2014.

3.2 Publication selection

In the search for systematic reviews and meta-analyses, 104 papers were identified, of which six were evaluated as potentially relevant based on titles and abstracts. After examination of the full text versions it was concluded that none of the papers were relevant for adverse effects of high doses in children and adolescents or based on new studies not included in the EFSA opinion (2012) or the IOM report (2011).

In the search for RCTs, 116 papers were identified, of which seven were identified as potentially relevant based on titles and abstracts. After examination of the full text versions it was concluded that four of the papers were relevant for adverse effects of high doses in

children and adolescents, and that two of these were studies included in the EFSA opinion (2012).

In the literature search for the role of vitamin D and bone formation and growth in children and adolescents, 48 papers were identified of which none were considered as relevant for the purpose of this statement.

4 Studies investigating high doses of vitamin D in children and adolescents

A common feature is that the retrieved studies have mainly included adolescents, while safety studies in children aged 1-10 years are absent. Moreover, in all studies the supplements are provided as bolus doses that are in some cases high, while the corresponding average daily dose is far below the UL proposed by EFSA. The studies are also described in more details in Summary Tables in Appendix 1.

4.1 The two studies included in EFSA's recent opinion on UL for vitamin D

El-Hajj Fuleihan et al. (2006)

This paper reported the results of a one year double-blind randomised trial with weekly oral high-dose vitamin D_3 to girls aged 10-17 years in Beirut, Lebanon (n=168). The objective was to assess whether high-dose vitamin D supplementation would enhance muscle and bone growth in puberty. The study was not specifically designed to assess safety of vitamin D supplementation. Boys were also included in the trial but according to the authors, results for boys are not reported due to null findings. One group (n=55) received a weekly oral dose of 350 µg vitamin D_3, corresponding to a daily average of 50 µg. The second group (n=58) received a weekly oral dose of 35 µg vitamin D_3, corresponding to a daily average of 5 µg. The third group (n=55) received placebo. Main outcome measures were percent changes in lean mass, areal bone mineral density (BMD) and bone mineral content (BMC) at the lumbar spine and total body, measured by dual-energy X-ray absorptiometry (DXA). Mean (SD) baseline serum 25-(OH)-vitamin D was 35 (20) nmol/L in the overall group. In the high-dose group, mean (SD) serum 25-(OH)-vitamin D after one year was 95 (78) nmol/L. Concerning safety, two girls had hypercalcaemia at one year follow-up, with serum calcium 10.8 and 11.1 mg/dL (2.70 and 2.78 nmol/L), respectively. These were both in the placebo group. In the high-dose vitamin D_3 group, three girls had high final 25-(OH)-vitamin D levels: 257, 402 and 487 nmol/L, but none of these had concomitant hypercalcaemia defined as serum calcium above 10.7 mg/dL (2.68 nmol/L). The dropout rate was 6% (n=11) and did not differ by treatment group. One girl dropped out at seven months because of the development of glomerulonephritis, documented by biopsy, and treated as poststreptococcal glomerulonephritis. The treatment code was broken, and she was in the low-dose vitamin D treatment group (35 µg/week). The average number of sick days was the same for all three treatment groups, averaging two days per year.

Concluding remark: One year supplementation with weekly single oral doses of 350 µg vitamin D_3 given as oil solution was not associated with adverse events in girls aged 10-17. However, the average daily vitamin D dose in this study was 50 µg, only half that of the UL for adolescents that are under consideration in the present statement.

Maalouf et al. (2008)

This paper reported safety of high-dose vitamin D_3 supplementation in Lebanese boys and girls aged 10-17 years. The data are from a short-term pilot study with eight weeks treatment followed by eight weeks observation off-treatment, as well as the one year study reported in the El-Hajj Fuleihan paper from 2006 (see above).

In the short-term pilot study, subjects received a weekly dose of 350 µg vitamin D_3 in oil (n=8) or ethanol solution (n=9) or a weekly placebo (n=9) for eight weeks. Serum 25-(OH)-vitamin D was measured at baseline, 2, 4, 6, and 8 weeks, and after 8 weeks off therapy, while serum calcium and 1,25-$(OH)_2$-vitamin D was measured at baseline, 8 weeks, and after 8 weeks off therapy. At eight weeks, three subjects had serum calcium above the upper limit of normal for their age (2.68 mmol/L): two had received placebo and one had received high-dose vitamin D_3 in ethanol. Three subjects on high-dose vitamin D_3 (one oil-solution; two ethanol-solution) had a serum 25-(OH)-vitamin D above 150 nmol/L at eight weeks.

In the long-term study, subjects were randomised to three groups receiving a weekly dose of 350 µg vitamin D_3 (n=115), 35 µg vitamin D_3 (n=114), or placebo (n=111), respectively. Serum 25-(OH)-vitamin D and 1,25-$(OH)_2$-vitamin D was measured at baseline and 12 months, while serum calcium was measured at baseline, six months, and 12 months. After one year, seven subjects had elevated serum calcium (>2.68 mmol/L). Five of these were in the placebo group, one in the low-dose group and one in the high-dose group. Five subjects in the high-dose group had 25-(OH)-vitamin D > 150 nmol/L at one year. Their individual levels were: 487, 402, 257, 172, and 157 nmol/L.

Concluding remark: There was no evidence of vitamin D intoxication, defined as elevations in both calcium and 25-(OH)-vitamin D concentrations in serum within the same individual, either in the short-term (eight weeks) or long term (one year). Although single doses of 350 µg were given, the average daily vitamin D dose was maximum 50 µg/day, corresponding to half of the updated UL set for adolescents.

4.2 Other studies investigating high doses of vitamin D in children and adolescents

Guillemant et al. (2001)

This was a randomised placebo-controlled trial performed in 57 healthy French male adolescents aged 13-16 years. The study was designed to investigate whether a bimonthly dosing regimen would maintain vitamin D status through winter. Subjects were recruited from a jockey training school north of Paris. The intervention group (n=29) received a bimonthly dose of 2500 µg vitamin D_3 as a phial of water-soluble oral solution for six months during late winter (end of September, November and January). Serum 25-(OH)-vitamin D and intact parathyroid hormone (PTH) were measured in the end of summer (September) and winter (March). The study was not designed to study safety. Blood samples for measurements of serum calcium were not drawn after administration of high-dose to monitor safety, but before the first dose and two months after the final dose. Serum-calcium was not reported.

Concluding remark: Administration of a bimonthly single oral dose of 2500 µg vitamin D_3 (corresponding to approximately 40 µg/day on average) did not result in any harmful events

in 13-16 year old French boys. The study is limited by its small sample size and relatively short duration. It was not designed to monitor changes in serum calcium levels shortly after administration of high-dose vitamin D_3, and it did not address chronic daily intakes exceeding UL.

Carnes, Quinn, Nelson, Jones, and Winzenberg (2012)

This was a short-communication reporting the results of a small double-blind RCT assessing the safety and efficacy of high-dose intermittent vitamin D supplementation in Australian adolescents of both genders aged 15-17 years. Vitamin D_3 was given orally once every six months as a dose of 7500 µg (n=7), 3750 µg (n=7), or placebo (n=8). The main outcome measure was increase in serum 25-(OH)-vitamin D during 12 months. Serum calcium was measured two weeks after the initial dose to monitor safety. No subjects developed hypercalcaemia, and there were no reports of adverse events.

Concluding remark: Administration of a single oral dose of vitamin D up to 7500 µg did not result in any harmful events in 15-17-year-olds. As noted by the authors, less common adverse events may not have been detectable in this small sample. The sample was very small, and the study did not address chronic daily intakes exceeding upper limits. The high-dose corresponded to an average intake of 40 µg/day which is far below the UL under consideration for the current statement.

4.3 Discussion: Vitamin D given as high bolus-doses

Vitamin D may be administered either as a daily, oral dose or as oral or parenteral supplementation at longer intervals, e.g. weekly, every second week or monthly. In the latter cases vitamin D is usually supplied as a high-dose bolus, and for comparisons these higher doses have been converted into daily doses. In the two studies underlying EFSAs current ULs at 50 and 100 µg/day to children (1-10 years) and adolescents (11-17 years), respectively, the investigators gave the study subjects weekly vitamin D supplementation (El-Hajj Fuleihan et al., 2006; Maalouf et al., 2008) and extrapolated these doses to daily intakes. In its 2002 report, SCF summarised data showing hypercalcaemia following high-dose bolus supplementation of vitamin D. It is therefore questionable whether data from high-dose supplementation of vitamin D can be reliably converted into daily intakes, at least in children.

5 Is the tolerance for vitamin D in children and adolescents increased due to growth?

High intakes of vitamin D are toxic and hypercalcaemia, nephrocalcinosis and kidney failure have been reported. Adopted UL for vitamin D from 2002 was changed in the new UL set by EFSA in 2012 where it was suggested that children and adolescents have higher tolerance for vitamin D than adults per kg body weight because of rapid growth and bone formation. As described in section 2.1, a literature search was performed to identify studies investigating the role of vitamin D in bone formation and growth in children and adolescents. However, no new studies were obtained that could provide information concerning whether tolerance for vitamin D in children and adolescents is increased due to growth.

On the contrary, the literature does not seem to suggest a dose-response relationship between bone formation and vitamin D levels in children during their growth period into adolescence and adulthood. The available evidence suggests that there may be no additional benefit on bone accretion in childhood and adolescence of vitamin D supplementation to children with baseline serum 25-(OH)-vitamin D levels above 50 nmol/L (Winzenberg & Jones, 2013).

Present knowledge does not indicate that children or adolescents have higher tolerance for vitamin D per body weight compared to healthy adults.

6 Data gaps

New, relevant studies to set new upper safe levels (i.e. ULs) for dietary intake of vitamin D for children and adolescents are missing. Bolus doses given in earlier studies among children and adolescents do not represent regular/chronic daily intakes. To be able to set UL for vitamin D for children and adolescents, clinical randomised controlled studies with high chronic (daily) vitamin D doses of 100 µg/day or higher for adolescents and 50 µg/day for children should be given for up to a year. As far as we are aware, no such studies have been performed. The children and adolescents should be monitored with respect to the concentration of serum 25-(OH)-vitamin D, hypercalcaemia and kidney function as well as bone mineralisation.

7 Answers to the terms of reference

In the EFSA opinion on the tolerable upper intake level (UL) of vitamin D from 2012, UL for vitamin D is set at 100 µg/day for adults and adolescents aged 11-17 years, and 50 µg/day for children aged 1-10 years, taking into account the smaller body size in the younger age groups.

EFSA stated that there is no reason to believe that children and adolescents in the phase of rapid bone formation and growth have a lower tolerance for vitamin D compared to adults. In children and adolescents with lower weight than adults this assumption actually implies that they must tolerate more vitamin D per kg body weight than adults.

The Norwegian Food Safety Authority requests the Norwegian Scientific Committee for Food Safety (VKM) to evaluate this assumption in the EFSA opinion. VKM is therefore requested to evaluate if there is scientific evidence that a UL at 50 µg/day for children (1-10 years) and 100 µg/day for adolescents (11-17 years) is safe.

The Norwegian Food Safety Authority requests VKM to answer the following questions:

1. What is the scientific evidence for the assumption in the EFSA opinion?

   In the literature search we could not retrieve any data supporting a higher tolerance to vitamin D in children and adolescents due to rapid bone formation and growth. Moreover, there is apparently no firm association between bone formation and vitamin D levels in children during their growth period into adolescence/adulthood.

2. Is there scientific evidence that a UL at 50 µg/day for children (1-10 years) and 100 µg/day for adolescents (11-17 years) is safe?

   We have not been able to identify any study that has examined safety issues and/or adverse effects of vitamin D supplementation in doses above 50 µg/day to these two target groups. No studies investigating high intakes of vitamin D in children 1-10 years were found.

   In the 2002 report from SCF, a UL at 25 µg/day for children aged 2-10 years, and 50 µg/day for adolescents aged 11-17 years (corresponding to the UL for adults at that time) were set. To the best of knowledge no serious, harmful effects have been reported for these doses of vitamin D.

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Appendix 1

Reference	**Guillemant J, Le HT, Maria A, Allemandou A, Pérès G, Guillemant S. Wintertime vitamin D deficiency in male adolescents: effect on parathyroid function and response to vitamin D_3 supplements. Osteoporos Int 2001; 12: 875-9**
Study design and type	RCT Subjects matched in pairs for height, weight and Tanner pubertal stage before randomised to intervention or control.
Objective	To study whether bimonthly oral dose of 2500 µg vitamin D_3 maintains vitamin D and PTH status throughout winter in healthy adolescents.
Intervention	Oral vitamin D_3 (2500 µg = 100 000 IU) bimonthly (a dose corresponding to average ~40 µg/day) at three specific periods (end of September, November and January), as a phial of water-soluble oral solution: n=29. Control group: n=28.
Number of participants, country and age	57 French male adolescents, 13-16 years old, all pupils of a jockey training school north of Paris (46 degrees N).
Health outcome, a definition of the health outcome and how it was measured	s-25-(OH)-vitamin D and s-iPTH measured in the end of summer (September) and winter (March). Total s-calcium and s-phosphate were measured.
Follow-up period, drop-outs	6 months (including three doses).
Results	s-25-(OH)-vitamin D dropped in the control group but remained stabled in the intervention group throughout winter. s-iPTH increased in the control group but remained stable in the intervention group throughout winter. No events of hypercalcaemia.
Conclusion	Vitamin D_3 supplements were sufficient to maintain the concentrations of both 25-(OH)-vitamin D and PTH at their basal post-summer levels (March) when measured 2 months after the last intake (September).
Relevance for our assessment purpose	Administration of a single oral dose of 2500 µg vitamin D_3 did not result in any harmful events in 13-16-year-old French boys.
Limitations	- small study - relatively short duration - does not address chronic daily intakes exceeding UL - not designed to study safety. Blood samples were not drawn shortly after administration of high-dose to monitor safety, but before the first dose and two months after the final dose. Calcium in blood measured, but not reported.

Reference	**J Carnes, S Quinn, M Nelson, G Jones and T Winzenberg: Intermittent high-dose vitamin D corrects vitamin D deficiency in adolescents: a pilot study. [Short Communication.] European Journal of Clinical Nutrition (2012) 66, 530–532**
Study design and type	Double-blind RCT.
Inclusion criteria	Serum 25-(OH)-vitamin D 12.5-50 nmol/L, otherwise healthy.
Objective	To assess the safety and efficacy of high-dose intermittent vitamin D supplementation in adolescents. The rationale is that dosing regimens of more than 2 months intermittency have not been tested earlier. (There is a premise that administering supplements like this can be useful in adolescents due to compliance issues.)
Intervention	300,000 IU (7500 µg) vitamin D_3 (6x50,000 IU tablets) orally once every 6 months (corresponding to an average of 40 µg per day) for 1 year, n=7 150,000 IU [3750 µg] vitamin D_3 (3x50,000 IU tablets and 3xplacebo) orally once every 6 months (corresponding to an average of 20 µg per day) for 1 year, n=7 Placebo (6xplacebo) orally once every 6 months for 1 year, n=8.
Number of participants, country and age	n=22 , Australia (Southern Tasmania), 15-17 years, both sexes.
Health outcome	Main outcome measure was serum 25-(OH)-vitamin D after 12 months. Regarding safety, serum calcium was measured two weeks after initial dose.
Follow-up period, drop-outs	12 months.
Results	Mean serum 25-(OH)-vitamin D after 12 months were: 63.0 nmol/L in the 7500 µg-group (one person still below 50), 41.1 nmol/L in the 3750-group, and 35.8 nmol/L in the placebo group. Highest single observation was ~150 nmol/L (high-dose group), second highest was 105 nmol/L (also high-dose group). At 2 weeks, mean serum calcium was similar in the three groups. No participants developed hypercalcaemia. There were no reported adverse events. The authors noted that "less common adverse events may not have been detectable in this small sample".
Conclusion	300 000 IU (7500 µg) of vitamin D 6-monthly may be a safe, effective regimen to correct mild-to-moderate vitamin D deficiency in adolescents within high-patient adherence.
Relevance for our assessment purpose	Administration of a single oral dose of vitamin D up to 7500 µg (n=7) or 3750 µg (n=7) did not result in any harmful events in 15-17-year-olds.
Limitations	- small study - did not address chronic daily intakes exceeding UL

Reference	**El-Hajj Fuleihan G, Nabulsi M, Tamim H, Maalouf J, Salamoun M, Khalife H, Choucair M, Arabi A, Vieth R. Effect of vitamin D replacement on musculoskeletal parameters in school children: a randomized controlled trial. The Journal of Clinical Endocrinology and Metabolism 2006; 91(2): 405-12.**
Study design and type	Randomised double-blind placebo-controlled trial. Randomisation stratified by socioeconomic status.
Inclusion criteria	Age range 10-17, a period critical for bone accretion. Healthy; absence of a history of any disorders or medications known to affect bone metabolism. For the current analysis: Female gender, pre- and post-menarcheal. Both genders were included in the trial but there were no positive findings in boys, thus the paper reports results for girls only.
Objective	To investigate whether treatment with high-dose vitamin D would optimise gains in muscle mass, BMD, and BMC in adolescent girls compared with low-dose vitamin D and placebo.
Intervention	High-dose group (n=55): Weekly oral dose of 1,400 IU (35 µg) vitamin D_3 as liquid oil solution – corresponding to an average daily dose of 5 µg. Low-dose group (n=58): Weekly oral dose of 14,000 IU (350 µg) vitamin D_3 as liquid oil solution – corresponding to an average daily dose of 50 µg. Placebo group (n=55): Weekly oral placebo oil.
Number of participants, country and age	Girls aged 10-17, Lebanon. Recruitment from four schools in the greater Beirut area to ensure geographic and socioeconomic representation. n=179 enrolled and randomised; 168 completed the study and included in intention to treat analysis.
Health outcome, a definition of the health outcome and how it was measured	Primary outcomes were 1-year percent change in lean mass, areal BMD and BMC at the lumbar spine and total body, measured by dual energy X-ray absorptiometry. Serum calcium, phosphorus, alkaline phosphatase and vitamin D metabolites were measured at baseline, 6 months, and 12 months.
Follow-up period, drop-outs	12 months. n=11 (6.1% of those randomised) did not attend the follow-up examination. Dropout rates did not differ by treatment group. Reasons included being afraid of needle sticks, unable to make appointments, disliking the taste of the medication, and changing their mind about the study.
Results (in relation to our purpose)	Baseline 25-(OH)-vitamin D: mean 35 ± 20 nmol/L. Final levels: High-dose: mean 95 ± 78 nmol/L; Low-dose: mean 42.5 ± 15 nmol/L; Placebo: mean 40 ± 20 nmol/L. Concerning safety: Two subjects (1.2%) had serum calcium levels above the upper limit of normal for children (10.7 mg/dL corresponding to 2.68 mmol/L; ref. Lockitch 1988) at 1 year: 10.8 and 11.1 mg/dL. These were both in the placebo group. Three subjects in the high-dose intervention group had high final 25-(OH)-vitamin D levels: 257, 402 and 487 nmol/L, but none of these had concomitant hypercalcaemia. One girl dropped out at 7 months because of the development of glomerulonephritis, documented by biopsy, and treated as poststreptococcal glomerulonephritis. The treatment code was broken, and she was in the low-dose vitamin D treatment group. The average number of sick days was the same for all three treatment groups, averaging 2 days per year.
Relevance for our assessment purpose	1-year supplementation with a weekly single oral dose of 350 µg vitamin D_3 given as oil solution was not associated with adverse events in girls aged 10-17.
Limitations	Although single doses of 350 µg were given, the average daily vitamin D dose was maximum 50 µg/day and did not approach the ULs that are under consideration in the present statement.

Reference	**Maalouf J, Nabulsi M, Vieth R, Kimball S, El-Rassi R, Mahfoud Z, El-Hajj Fuleihan G. Short- and long-term safety of weekly high-dose vitamin D_3 supplementation in school children. J Clin Endocrinol Metab 2008; 93(7): 2693-701.**
Study design and type	Two randomised placebo-controlled trials: One single-blinded short-term pilot study with high-dose vs. placebo, and one double-blinded long-term study with high-dose, low-dose and placebo.
Inclusion criteria	Age 10-17 years; no disorders or medications known to affect bone metabolism.
Objective	To assess short-term and long-term safety of high-dose vitamin D supplementation in adolescents. The high-dose represented half the dose that is considered safe in adults and results in desirable 25-(OH)-vitamin D levels.
Intervention	*Short-term study:* Pilot to the long-term study (below), single blinded. Three groups: • High-dose in oil solution (n=8): Weekly dose of 350 µg for 8 weeks – corresponding to average daily dose of 50 µg • High-dose in ethanol solution (n=9): Weekly dose of 350 µg for 8 weeks – corresponding to average daily dose of 50 µg • Placebo (n=9): Weekly placebo *Long-term study:* • High-dose (n=115): Weekly dose of 350 µg for 12 months – corresponding to average daily dose of 50 µg • Low-dose (n=114): Weekly dose of 35 µg for 12 months – corresponding to average daily dose of 5 µg • Placebo (n=111): Weekly placebo
Duration	Short-term: 8 weeks treatment followed by 8 weeks off therapy. Long-term: 12 months treatment.
N participants, country and age	Short-term study: 25 boys and girls aged 10-17 years. Long-term study: 340 boys and girls aged 10-17 years. Recruited from four schools in the Beirut area, Lebanon.
Health outcome, a definition of the health outcome and how it was measured	*Short-term study:* Serum 25-(OH)-vitamin D measured at baseline, 2, 4, 6, and 8 weeks, and after 8 weeks off therapy. Serum calcium and 1,25-$(OH)_2$-vitamin D measured at baseline, 8 weeks, and after 8 weeks off therapy. Blood collection took place fasting, right before the due weekly dose of vitamin D. *Long-term study:* Serum 25-(OH)-vitamin D and 1,25-$(OH)_2$-vitamin D measured at baseline and 12 months. Serum calcium measured at baseline, 6 months, and 12 months. Blood collection did not take place with any specific timing in relation to the last dose of vitamin D received.
Drop-outs	Long-term study: 12 boys (6.5%) and 11 girls (9.8%) dropped out. There were no differences in dropout rates by treatment group in either sex. The reasons for dropout included being afraid of needle pricks, unable to make appointments, not liking the taste of the medication, and changing their mind about the study. One girl in the low-dose vitamin D treatment group dropped out at 7 months because of development of glomerulonephritis, documented by biopsy, and treated as poststreptococcal glomerulonephritis.

Results

Short-term study: High-dose group: Mean 25-(OH)-vitamin D increased from 110 (SD 27) to 135 (SD 47) nmol/L (p=0.033). There were no significant differences in serum calcium levels achieved at 8 weeks, or 8 weeks off therapy between the groups. At 8 weeks, 3 subjects had serum calcium above the upper limit of normal for their age (2.68 mmol/L): two had received placebo and one had received high-dose vitamin D_3 in ethanol. 3 subjects on high-dose vitamin D_3 (one oil-solution; two ethanol-solution) reached a serum 25-(OH)-vitamin D above 150 nmol/L at 8 weeks. None had evidence of vitamin D intoxication, defined as frank elevations in both serum calcium and 25-(OH)-vitamin D levels.

	Treatment	Ca (mmol/L)	25-(OH)-vitamin D nmol/L	$1,25\text{-}(OH)_2$-vitamin D pmol/L
Elevated Ca at 8 weeks	Placebo	2.85	125	195
	Placebo	2.73	65	130
	350 µg vit D_3 in ethanol	2.70	195	237
High 25-(OH)-vitamin D at 8 weeks	350 µg vit D_3 in oil	2.58	240	148
	350 µg vit D_3 in ethanol	2.48	215	182
	350 µg vit D_3 in ethanol	270	195	237

Long-term study: Low-dose group: Mean 25-(OH)-vitamin D increased from 37.5 (SD 20) to 47.5 (SD 17.5) nmol/L (p<0.0001)
High-dose group: Mean 25-(OH)-vitamin D increased from 37.5 (SD 17.5) to 90 (SD 55) nmol/L (p<0.0001)
7 subjects had elevated Ca (>2.68 mmol/L) at 1 year; 5 of these were in the placebo group, 1 in low-dose group and 1 in high-dose group.
5 subjects had 25-(OH)-vitamin D > 150 nmol/L at 1 year, these were all in the high-dose group.

	Treatment	Ca (mmol/L)	25-(OH)-vitamin D nmol/L	$1,25\text{-}(OH)_2$-vitamin D pmol/L
Elevated Ca at 12 months	Placebo	2.78	22	-
	High-dose	2.75	80	268
	Low-dose	2.73	57	234
	Placebo	2.70	52	341
	Placebo	2.70	32	200
	Placebo	2.70	60	247
	Placebo	2.70	40	130
High 25-(OH)-vitamin D at 12 months	High-dose	2.60	487	91
	High-dose	2.63	402	182
	High-dose	2.43	257	70

		High-dose	2.63	172	255
		High-dose	2.48	157	377
Relevance for our assessment purpose	Vitamin D_3 at doses equivalent to 50 µg/day for one year was well tolerated and led to desirable 25-(OH)-vitamin D levels in adolescents aged 10-17. There was no evidence of vitamin D intoxication, defined as frank elevations in both serum calcium and 25-(OH)-vitamin D levels within the same individual, either in the short-term or long term study.				
Limitations	Although single doses of 350 µg were given, the average daily vitamin D dose was maximum 50 µg/day corresponding to half of the current UL.				