Committee on toxicity of chemicals in food, Consumer products and the environment

The potential effects that excess vitamin D intake may have during preconception, pregnancy and lactation. Third draft statement.

Background

1. The Scientific Advisory Committee on Nutrition (SACN) last considered maternal diet and nutrition in relation to offspring health in its reports on 'The influence of maternal, fetal and child nutrition on the development of chronic disease in later life' (SACN, 2011) and on 'Feeding in the first year of life' (SACN, 2018). In the latter report, the impact of breastfeeding on maternal health was also considered. In 2019, SACN agreed to conduct a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery; this would include the effects of chemical contaminants and excess nutrients in the diet.

2. SACN agreed that, where appropriate, other expert Committees would be consulted and asked to complete relevant risk assessments e.g. in the area of food safety advice. A provisional list of chemicals was proposed by SACN and updated and amended following discussions by COT who will be guiding the toxicological risk assessment process.

3. The COT was asked to consider whether exposure to excess vitamin D would pose a risk to maternal health in discussion paper (TOX/2021/08)[1] and in a draft statement (TOX/2020/20)[2].

UV exposure and serum 25(OH)D

4. The Committee concluded that the relationship between oral vitamin D intake and serum 25(OH)D as well as UV exposure and serum 25(OH)D levels are unclear and not known due to many uncertainties and has been reflected in Annex A.

5. Members requested that is should be highlighted that consumption from vitamin D containing supplements alone is sufficient to result in exceedance of the Tolerable upper level (TUL), and that consumption of dietary sources of vitamin D and supplements combined are likely to result in higher exposure levels.

[1] TOX/2021/08 is available on the COT website
[2] TOX/2021/20 is available on the COT website

Exposure assessment

6. Table 4 has been added to the exposure assessment section. It shows comparisons of vitamin D exposure from different sources (food sources (excluding supplements), supplements only and food sources (including supplements)) and indicates that food supplements are likely to be the biggest contributor to vitamin D exposure.

7. Clarification on the uncertainties around the use of women of child-bearing age (16-49 years) to construct exposure assessments has been provided.

Other new information

8. A section has been added on Stoss therapy (paragraphs 19-2) where single or intermittent high doses of vitamin D have been used to treat deficiency.

9. The committee also suggested looking for studies using high bolus vitamin D doses to treat women with early onset osteoporosis[3]. However, no trials administering high doses of vitamin D in younger women with osteoporosis were identified in the literature by the secretariat. Two randomised controlled trials (Burt et al., 2019; Harwood et al., 2004) that administered doses between 10-7,500 µg (400-300,000 IU) in healthy adults and adults that have had hip fractures, aged 55 years and over are discussed in paragraphs 24-25.

10. The Committee are asked to consider the draft statement attached at Annex A which includes further information as described above. New text is highlighted in yellow.

Questions for the Committee

Members are asked to consider the following questions:

a) Do Members have any comments on the relationship between UV exposure and serum vitamin D levels?
b) Do Members have any comments on the relationship between oral vitamin D intake and serum vitamin D levels?
c) Do Members have any comments on the new text in this statement?
d) Do Members have any other comments on the structure and content of the statement?

Secretariat

October 2021

[3] COT Final minutes May 2021 is available on the COT website

Annex A to TOX/2021/50

COM Committee On Toxicity Of Chemicals In Food, Consumer Products And The Environment (COT)

Third draft statement paper on the potential effects of excess vitamin D intake during preconception, pregnancy and lactation.

Introduction

1. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked to consider whether exposure to excess vitamin D would pose a risk to maternal health, in support of a review by the Scientific Advisory Committee on Nutrition (SACN) of nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery; including the effects of chemical contaminants and excess nutrients in the diet.

Background

2. Vitamin D refers to two lipid-soluble substances termed *seco*-steroids. One of these (vitamin D_2 or ergocalciferol) is of plant and fungal origin and thus is only accessible to humans via the diet. The other *seco*-steroid (vitamin D_3 or cholecalciferol) is synthesised in mammalian skin by the ultraviolet-B photolysis of the steroid 7-dehydroxycholesterol (7-DHC) or is obtainable by the consumption of oil rich foods or supplements of animal origin such as cod liver oil. As discussed in paragraph 40 and 44; 7-DHC is produced endogenously in the skin, but can also been found in the leaves of plant species belonging to the Solanaceae family (which includes vegetables such as potato, tomato and pepper). The leaves of these plants are not commonly consumed, therefore contribution of 7-DHC from the diet is likely to be very small.

3. Since vitamin D can be synthesised internally and is metabolised to the active form by the liver and kidney and can regulate the transcription of vitamin D responsive genes and blood calcium concentration (Morris, 2005), it is often referred to in the literature as a hormone, rather than a vitamin.

Vitamin D function and status

4. Vitamin D is important for musculoskeletal health as it regulates calcium and phosphorous metabolism, which is required for normal bone mineralisation, muscle contraction, nerve conduction and general cellular function in all cells in the body.

Other possible functions involve a role in the immune system due to the wide distribution of vitamin D receptors on various cells of the immune system. Vitamin D may also play a role in regulation of cell proliferation, cell differentiation and apoptosis as vitamin D-responsive elements are present in a large number of genes associated with these cellular processes (COT, 2014).

5. When absorbed or released into systemic circulation, both forms of vitamin D are transported to the liver by Vitamin D Binding Protein (DBP), where they are hydroxylated by cytochrome P450 (CYP) 2R1 to 25-hydroxyvitamin D (25(OH)D), which has a long half-life (about 2-3 weeks) in blood plasma and is widely used as a biomarker for an individual's vitamin D status.

6. The 25(OH)D is then secreted from the liver into the systemic circulation, where it binds to DBP. When the bound 25(OH)D reaches the kidneys, it is further hydroxylated to the hormonally active product 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) by CYP27B1.

7. Vitamin D is lipid soluble, and fat deposits in the body are the major site of vitamin D storage. Excess vitamin D consumption can lead to elevated circulating concentrations and possible toxicity (Holick et al., 1981).

8. As noted in the SACN 2016 vitamin D report: "prolonged UVB exposure results in conversion of previtamin D_3 to lumisterol and tachysterol which are biologically inactive (Holick et al., 1981). Cutaneous vitamin D_3 can also isomerise into a variety of photoproducts such as suprasterol I, suprasterol II and 5,6 transvitamin D_3 (Webb et al., 1989). "These photoconversions, which are reversible if concentrations of previtamin D3 fall, prevent accumulation of toxic amounts of vitamin D_3 from cutaneous exposure alone" (Holick et al. 1980).

9. Serum 25(OH)D concentration is an indicator of an individual's long-term vitamin D status. Circulating levels of 25(OH)D in the blood are normally in the range of 25-200 nmol/L (COT, 2014) but Hollis, 2005 reported circulating levels of 135 to 225 nmol/L in sunny environments where clothing or cultural practices do not prevent sun exposure (COT, 2014). In the UK, evidence of a low vitamin D status has been demonstrated in the results of years 9 to 11 of the National Diet and Nutrition Survey (NDNS); 16% of adults aged 19-64 years had a serum 25-(OH)D concentration less than 25 nmol/L between 2016 and 2019 (Bates et al., 2020). However, it is important to note that the relationship between serum 25(OH)D levels and oral vitamin D, as well as serum 25(OH)D levels and UV exposure and serum 25(OH)D levels are unclear. This is due to many uncertainties such as season, time, of day, amount of skin exposed, skin pigmentation and use of SPF sunscreen.

Vitamin D status in pregnancy

10. There is a lack of data on what constitutes a healthy vitamin D status in pregnant women. The functions of vitamin D include regulating the metabolism of calcium and phosphate, which is essential for bone mineralisation (COT, 2014). However, there is no agreement on whether requirements for 25(OH)D are higher during pregnancy compared to non-pregnant adults (Kiely et al., 2020). SACN (2016)

did not recommend a separate reference nutrient intake (RNI) for pregnant women, as the RNI of 10µg/day (400 IU/day) is inclusive of pregnant and lactating women.

11. Clinical trials involving vitamin D supplementation showed the conversion of vitamin D to 25(OH)D appears unchanged (Wagner et al., 2012) or was slightly lower during pregnancy (Kovacs, 2008). This suggests that 25(OH)D levels remain stable during pregnancy (Kovacs, 2008) and the increase in serum 25(OH)D concentration in response to vitamin D supplementation of pregnant and lactating women is similar to that of non-pregnant or non-lactating women (SACN, 2016).

12. However, a number of studies have reported the conversion of 25(OH)D to $1,25(OH)_2D$ during the first trimester (12 weeks of pregnancy) as unique to pregnancy; $1,25(OH)_2D$ levels double and continue to rise 2 to 3-fold from a non-pregnant adult baseline to over 700 pmol/L (0.7 nmol/L)[4], until delivery without the onset of hypercalciuria or hypercalcemia (Hollis et al., 2017; Heaney et al., 2008; Kovacs, 2008). The increase in $1,25(OH)_2D$ observed during pregnancy is not continued throughout lactation (Hollis and Wagner, 2017). Hollis et al. (2011) demonstrated that circulating levels of approximately 40 ng/ml (100 nmol/L)[5] of 25(OH)D are required to optimize the production of $1,25(OH)_2D$ during human pregnancy via renal and/or placental production. Pregnant women with normal placental function but non-functional renal enzyme 1-α-hydroxylase fail to increase circulating 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) during pregnancy (Greer et al., 1984).

13. 25(OH)D is transported via the placenta to the fetus and also converted there to $1,25(OH)_2D$ or 24,25-dihydroxyvitamin D ($24,25(OH)_2D$) (discussed EFSA, 2018).

14. In lactating women, elimination of vitamin D via breast milk accounts for a small percentage of the overall elimination. Vitamin D passes more readily from circulation into breast milk than 25(OH)D and concentration of vitamin D in breast milk is higher than 25(OH)D and $1,25\ (OH)_2D$ (EFSA, 2016).

Excess vitamin D – human health studies and case reports

15. Hypervitaminosis D (excess vitamin D) can lead to hypercalcaemia[6], causing deposition of calcium in soft tissues, demineralisation of bones and irreversible renal and cardiovascular toxicity. Hypercalcaemia has been reported at plasma 25(OH)D concentrations above 375-500 nmol/L (SACN, 2016). Hypercalcaemia can also lead to hypercalciuria[7] (EVM, 2003).

16. High oral doses of vitamin D supplements have been shown to have toxic effects, such as hypercalcaemia, dehydration and tissue calcification (Vieth, 2006).

[4] 1 pmol/L = 0.001 nmol/L
[5] 1 ng/mL = 2.5 nmol/L
[6] Hypercalcaemia is generally defined as a total calcium concentration greater than 2.75 mmol/L.
[7] Hypercalciuria is defined as being when urinary excretion of calcium exceeds 250 mg/day in women and 275-300 mg/day in men.

After a 1951 survey for the UK Ministry of Health showed that some children were receiving up to 35,000 IU per day (875 µg/day) due to supplementation and fortification of foods, vitamin D intakes in national cod-liver compounds and dried milk were halved in 1957. Following the reduced intake there was a marked decrease in the number of infantile hypercalcaemia cases in the early 1960s (EVM, 2002).

17. Vomiting, nausea, constipation, and diarrhoea were reported as symptoms of vitamin D overdosing in Danish infants who consumed a liquid vitamin D supplement that contained 150 µg of vitamin D_3 per drop instead of the indicated level of 2 µg per drop (Stafford, 2016). The recommended daily dose of this product was 5 drops therefore infants that consumed this supplement received 750 µg/day (Tetens et al., 2018) and exceeded the Danish Health and Safety Executive's recommended daily supplement intake of 8.5-10µg for vitamin D for babies who do not consume 500 ml of infant formula per day (Mayor, 2016).

18. The Danish Health Authorities identified 18/150 children (under the age of 2) who had consumed this vitamin D supplement, and had severe hypercalcemia with ionized calcium levels of >1.49 mmol/L. As for elevated 25(OH)D levels, these were >150 nmol/L in 87/150 children that had consumed the supplement (Tetens et al., 2018).

19. Stoss therapy is a single high oral or intramuscular dose of vitamin D administered at 2,500 -15,000 µg (100,000 – 600,000 IU) to treat vitamin D deficiency, the dose administered is dependent on the age and vitamin D level of the patient used (Çağlar and Çağlar, 2021).

20. In a retrospective study of case reports over a 5-year period, 38 patients aged 0.3-4 years presented with vitamin D intoxication (vomiting, loss of appetite and constipation) and hypercalcemia (mean calcium levels were 3.75 ± 0.5 mmol/L) after consumption of either a prescribed vitamin D_3 vial for stoss therapy, non-prescribed vitamin D_3 vials or incorrectly produced fish oil. The vials contained 7,500 µg (300,000 IU) of vitamin D_3, the 9 patients using these vials without prescription were exposed to 15,000-45,000 µg (600,000-2,400,00 IU) of vitamin D. In the 23 patients prescribed these vials for stoss therapy, their exposure was between 15,000-60,000 µg (600,000-I,800,000 IU) of vitamin D. It is unclear how soon after receiving stoss therapy vitamin D intoxication occurred. The patients who had consumed improperly produced fish oil supplements containing 400,000 µg (16,000,000 IU) of vitamin D_3 per bottle, were exposed to 25,000-50,000µg (1,000,000 – 2,000,000 IU). The duration of consumption of the fish oil supplements is unclear. The researchers determined that minimum dose of vitamin D received that caused vitamin D intoxication was 15,000µg (600,000 IU) and at the time of admission serum 25(OH)D levels were 990 ± 275 nmol/L (396 ± 110 ng/mL) (Çağlar and Çağlar, 2021).

21. Other studies of stoss therapy using lower doses of vitamin D have not reported adverse effects such as hypercalcemia or hyperphosphatemia (elevated phosphate in the blood). In a randomized single-blind clinical trial, there were no adverse effects from stoss therapy 3 weeks after treatment in children aged 2.5 to 6 years with serum 25(OH)D levels of <50 nmol/L (20 ng/mL). Children were either treated with 10g fortified biscuits or with vitamin D capsules containing 1,250 µg

(50,000 IU) of vitamin D_3 twice per week for a period of 3 weeks. The remaining treatment group received a single ampoule dose containing 7,500µg (300,000 IU) of vitamin D via injection. After treatment, mean serum 25(OH)D levels increased to 143.65 ± 77.65 nmol/L (57.46 ± 31.06 ng/mL) in those that received an ampoule dose via injection; 118 ± 62.15 nmol/L (47.20 ± 24.86 ng/mL) in those that received vitamin D capsules and 98.9 ± 53.75 nmol/L (39.52 ± 21.50 ng/mL) in those that received fortified biscuits. Baseline 25(OH)D levels were only reported for subjects in the pre-protocol analysis group that excluded those who did not complete the treatments. Mean baseline serum 25(OH)D levels were 40 nmol/L (16.39 ng/mL), in those receiving ampoule dose via injection; 39.85 nmol/L (15.94 ng/mL) in those receiving vitamin D capsules and 41.225 nmol/L(16.49 ng/mL) in those receiving fortified biscuits (Moslemi et al., 2018).

22. In another study assessing the safety and efficacy of stoss therapy in 37 children with cystic fibrosis and vitamin D deficiency (defined as serum 25(OH)D ≤25 to ≤75 nmol/L) children between the ages of <3 to >12 years were administered doses of 2,500 to 15,000 µg. Serum 25(OH)D levels increased up to 94.82 ± 41 nmol/L, 81.54±24.6 nmol/L, 92.18±36.5 nmol/L and 64.6±20 nmol/L 1, 3, 16 and 12 months post treatment respectively, and no evidence of vitamin D toxicity such as hypercalcaemia, hyperphosphatemia (elevated phosphate in the blood) was observed. (Shepherd et al., 2013).

23. SACN, (2016) reported a number of intoxication cases that occurred as a result of high medicinal doses or excessive or mis-formulated supplement use to be associated with serum 25(OH)D levels of as low as 300 nmol/L, but often exceeding 1000 nmol/L; the SACN report was based on a review by the COT (COT, 2014) . In this, COT noted that the doses of vitamin D consumed in these cases ranged from 750-1,500,000 µg (30,000-60,000,000 IU) and the duration of consumption ranged from 4 days –10 years. However, other evidence in humans based on anecdotal case reports of acute accidental vitamin D intoxication resulting in plasma 25(OH)D concentrations of 710-1587 nmol/L, with a threshold for toxic symptoms around 750 nmol/L has been reported by Vieth, 1990. It is important to note that a threshold for toxicity was not proposed by SACN or COT as the case reports provide limited information for risk assessment purposes as the doses consumed, where known, have varied in amount and duration.

24. A recent randomised controlled trial (RCT) assessed the effect of vitamin D supplementation on volumetric bone mineral density (BMD) in healthy men and women without osteoporosis aged 55-70 years. Participants were given daily oral doses of vitamin D for 3 years at 10 µg (400 IU), 100 µg (4,000 IU) and 250 µg (10,000 IU). The percentage of participants that reported hypercalcemia as an adverse event was 33% in those receiving 250 µg (10,000 IU) compared to 22% in those received 100 µg (4,000 IU). The percentage of participants reporting renal dysfunction, nephrolithiasis, hepatic dysfunction was 2%, 1% and 3% respectively for both groups receiving 250 µg (10,000 IU) and 100 µg (4,000 IU). Whereas low-trauma fractures were reported by 5% of patients in the 250 µg (10,000 IU) compared to 2% in the 100 µg (4,000 IU) group. Despite the various reporting of adverse events the study authors made no conclusions on the harmful effects of vitamin D. This was because the measurements of volumetric BMD were in the opposite direction of the hypothesised effect and was considered inappropriate to

interpret findings as proof of skeletal harm. Ultimately, the study authors concluded that further research is required to determine if high-dose vitamin D is harmful (Burt et al., 2019).

25. Another RCT; the Nottingham Neck of Femur (NoNOF) study compared calcium and vitamin D supplementation regimens in 150 women aged 67-92 years after experiencing hip fracture. Participants either received a single injection of 7,500 µg (300,000 IU) of vitamin D_2, injected vitamin D_2 + 1 g/day oral calcium, 800 units/day oral vitamin D_3 + 1 g/day calcium, or no treatment. After a 1 year follow up, the study authors reported that there were no cases of hypercalcaemia and no participants were withdrawn because of adverse effects of any of the aforementioned study medication (Harwood et al., 2004).

26. Vitamin D toxicity is not thought to occur following UV exposure as serum vitamin D does not rise to potentially toxic levels. The National Institute for Health and Care Excellence (NICE) have noted various studies (Rhodes et al., 2010; Binkley et al., 2007) which report 25(OH)D levels to "plateau at around 70 – 80 nmol/L after UV exposure, with wide variation across individuals" (NICE, 2021). The 25(OH)D levels achievable via UV exposure are 4 times lower than the lowest 25(OH)D levels associated with toxicity and ten times lower than the threshold for toxic symptoms of 750 nmol/L proposed by Vieth, (1990).

27. Vitamin D_2 has been reported to be less potent than vitamin D_3, (Heaney, 2008) with its potency being one third of vitamin D_3 (Armas et al., 2004). Other sources report vitamin D_3 as 87% more potent in raising and maintaining serum 25(OH)D levels (Heaney et al., 2011).

28. Proposed mechanisms of toxicity are based on the over-expression of vitamin D-responsive genes in the nucleus of target cells, induced by 25(OH)D or $1,25(OH)_2D$ (Jones, 2008).

Preconception

29. There is currently no evidence on the effect of excess vitamin D during preconception. A number of studies have examined the potential beneficial effects of vitamin D prior to conception. For example, vitamin D intake of up to 10 µg/day (400 IU) and higher blood vitamin D concentrations (between 75 - 125 nmol/L) during preconception have been associated with increased fecundability (Jukic et al., 2019), reduced risk of pregnancy loss (Mumford et al., 2018 abstract only) and reduced risk of gestational diabetes mellitus (Bao et al., 2018). These studies have not been considered further, however; such supplement studies have not reported obvious adverse effects.

Pregnancy

30. Data on high levels of vitamin D intakes during pregnancy or lactation are lacking (SACN, 2016). No adverse effects were observed in 2 studies (Wagner et al., 2006; Hollis et al., 2011) which supplemented pregnant women with vitamin D doses ≥ 100 µg/day (4000 IU). Additionally, the COT previously noted that "serum calcium

has not always been measured in such studies and where it was done, hypercalcaemia was not observed" (COT, 2014). However, there is potential for hypercalcemia to occur during pregnancy in individuals with mutations of genes involved in vitamin D metabolism.

31. A recent paper reported a case of a pregnant woman with disordered vitamin D metabolism due to a loss of function CYP24A1 mutation who was supplemented with cholecalciferol (vitamin D) at 1,250 µg/month (50,000 IU/month) and presented with symptomatic hypercalcemia (Macdonald et al., 2020). In an earlier case study, a patient with recurrent hypercalcemia and elevated 1,25-$(OH)_2$D and 25(OH)D levels during pregnancy showed CYP24A1 mutations (Shah et al., 2015). In a further case study, the occurrence of hypercalcemia was associated with vitamin D intake at the recommended dose of 10 µg/day (400 IU/day) in pregnant women and infants (from two separate families) with loss of function CYP24A1 mutations) after delivery (Dinour et al., 2015). It has been reported that "estimates of the frequency of CYP24A1 gene mutations suggest 1:100 carriers and a 1:40 000 incidence of" idiopathic infantile hypercalcemia (Jones, 2016 Symposium abstract). Earlier reports have estimated the incidence of idiopathic infantile hypercalcemia to be 1 per 47,000 total live births in the United Kingdom (Martin et al., 1984).

32. Polymorphisms in the Vitamin D receptor have also been reported, but these have been associated with increased susceptibility to conditions that are a result of low vitamin D such as rickets, hypocalcaemia (Malloy and Feldman, 2012), preeclampsia, fetal growth restriction and diabetes in pregnancy (Knabi et al., 2017). VDR polymorphisms may therefore be more likely to contribute to vitamin D deficiency rather than an excess.

33. Excessive vitamin D intake during pregnancy can also result in risk of foetal hypercalcemia (Larquè et al., 2018), and hypercalcemia during pregnancy may be associated with increased risk of foetal and neonatal morbidity (Sato, 2008); this aforementioned statement from Sato, 2008 appears to be based on case reports, but limited details are provided. Additionally, neonatal hypercalcemia has been evident in neonates born to mothers with an excess maternal vitamin D intake. In a case reported by Reynolds et al. (2017), a female baby was diagnosed with hypercalcemia with 25(OH)D levels of 72 nmol/L, which was at the upper end of the reference range (50-75 nmol/L). The baby also had total serum calcium levels of 3.09 nmol/L, which was outside the reference range of 1.9-2.6 nmol/L. While the mother, after taking two supplements resulting in a total daily vitamin D_3 intake of 4000 IU, was reported to have elevated 25(OH)D levels of 127 nmol/L, which was slightly outside the reference range (> 125 nmol/L). The mother also had total serum calcium levels of 2.38 mmol/L which was within the reference range of 2.1-2.66 nmol/L.

34. Other potential adverse effects of vitamin D intake may include increases in blood pressure as has been reported in some RCTs. Healthy pregnant women in Bangladesh were administered doses of vitamin D that were equivalent to the tolerable upper limit (TUL) of 100 µg/day (EFSA, 2012) (700 µg/week, equivalent to 28,000 IU/week) and showed higher maternal blood pressure than the placebo group at 30-36 weeks of gestation. However, the increases in blood pressure were not clinically classified as hypertension and many of the participants started the trial with

low blood pressure. The mean difference in systolic blood pressure was 0.2 mmHg (CI = -0.1 to 0.5) and diastolic blood pressure was 0.2 mmHg (CI = -0.0 to 0.4). However, the mean serum 25(OH)D levels of participants in this treatment group were low; 26.7 nmol/L (Subramanian et al., 2021), which was defined as deficient by the study authors (i.e. <30 nmol/L of 25(OH)D) However, it should be noted that the 2016 SACN report on vitamin D and health states that "it is recommended that the serum 25(OH)D concentration of all individuals in the UK should not fall below 25 nmol/L at any time of year", therefore the level noted in the aforementioned study, although low, is not considered deficient by (SACN, 2016) and as discussed in paragraph 36, these levels would not be unusual in south Asian ethnicities in the UK during winter.

Lactation

35. Although there is very limited evidence for adverse effects relating to vitamin D consumption during lactation, Roth et al., (2018) reported that there was a high rate of "possible hypercalciuria" among the women in Bangladesh receiving the highest dose of 700 µg/week (28,000 IU/week) in a randomized double-blind, placebo-controlled trial. "Possible hypercalciuria" was defined as a single urinary calcium: creatinine ratio of >1, with both calcium and creatinine measured in millimoles (>0.35, with both measured in milligrams). Participants in this category had mean 25(OH)D serum levels of 26.6 nmol/L, which is lower than those considered deficient by study researchers, but, as noted above, is not considered deficient by SACN, 2016.

Health based guidance values

36. As noted above, in 2016, SACN set a reference nutrient intake (RNI) of 10 µg/day (400 IU/d) for the general population which included pregnant and lactating women and population groups at increased risk of having a serum 25(OH)D concentration <25 nmol/L (SACN, 2016).

37. In 2003, the UK Expert Group on Vitamins and Minerals (EVM) concluded that there was insufficient information to establish a Safe Upper Level (SUL) for vitamin D but noted that for guidance purpose only, intakes of 25 µg/day (1000 IU/d) supplementary vitamin D would not be expected to result in adverse health effects (EVM, 2003).

38. The European Food Safety Authority (EFSA) reviewed vitamin D in 2012 and established a Tolerable Upper Limit (TUL) of 100 µg vitamin D per day for adults and 25, 50 and 100 µg/day vitamin D for infants and children aged up to 12 months, 1-10 years and 11-17 years respectively. EFSA recognized that D_3 may raise 25(OH)D levels more than D_2, however, as the UL of 100 ug/day was supported by 2 studies both using D_2 and D_3, EFSA's TUL was protective of both forms of vitamin D (D_2 and D_3). The TUL was also not adjusted to take into account pregnancy or lactation as a TUL is intended to apply to all groups of the general population, including individuals, in more sensitive stages of life such as pregnancy. However, the TUL does not cover cases of discrete, identifiable sub-populations who may be especially vulnerable to

one or more adverse effects (for example, due to unusual genetic predisposition, certain diseases, or receiving the vitamin under medical supervision) (EFSA, 2006).

39. The COT agreed that the EFSA TUL of 100 µg/day (4000 IU/day) set for adults (≥ 18 years) was appropriate for pregnant and lactating women (SACN, 2016).

Vitamin D exposures in maternal health

Sources of vitamin D exposure

Ultraviolet (UV) radiation

40. For most people, vitamin D_3 formation by exposure to UVB radiation is the main source of vitamin D. There are many factors affecting vitamin D formation such as season, time of day, amount of skin exposed, skin pigmentation and use of SPF sunscreen and this is reflected in the NHS Consensus Vitamin D position that states "there is still a lot of uncertainty around…how much sunlight different people need to achieve a given level of vitamin D" (NHS, 2010). However, Rhodes et al., 2010, reported that white-skinned adults exposed to UV radiation at a dose equating to 15 minutes, 6 times a week during winter had mean 25(OH)D levels of 70 nmol/L. Additionally, a longitudinal study (Webb et al., 2011) reported that white-skinned adults had vitamin D levels of 71 nmol/L in September and 45.8 nmol/L in February, when spending mean daily time of 9 minutes/day outdoors on weekdays and 18 minutes/day on weekends (SACN, 2016). In another longitudinal study (Kift et al., 2013), white adults had median serum 25(OH)D levels of 65.4 nmol/L in summer and 47.2 nmol/L in winter. Whereas adults of south Asian ethnicity had median serum 25(OH)D levels of 22.5 nmol/L in summer and 14.5 nmol/L in winter (SACN, 2016). Additionally, the most recent NDNS survey reported mean and 97.5th percentile serum 25(OH)D levels of 48.4 and 98.9 nmol/L respectively amongst females aged 19-64 years (Bates et al., 2020).

41. "It is important to note that prolonged sunlight exposure does not lead to excess production of cutaneous vitamin D because endogenously produced pre-vitamin D_3 and vitamin D_3 are photolyzed to inert compounds. Vitamin D_3 is produced endogenously from 7-dehydrocholesterol (7-DHC) in the skin of humans and animals by the action of sunlight containing UVB radiation (wavelength 280-315 nm) or by artificial UVB light. The 7-DHC in the epidermis is converted to pre-vitamin D_3, which reaches a maximum concentration in the skin within a few hours (Holick et al., 1980). Even with prolonged irradiation in sunlight the amount of pre-vitamin D formed is limited to 12-15% of the original 7-DHC (MacLaughlin et al., 1982; Webb et al., 1988)" (SACN citing Hollick et al.,1980; MacLaughlin et al., 1982; Webb et al., 1988).

Food

42. In the UK, the main dietary sources of vitamin D are foods of animal origin, fortified foods and supplements (SACN, 2016).

43. There are limited sources of vitamin D_2 from food. Wild mushrooms are a rich natural source, containing 13-30 µg (520-1200 IU) per 100 g fresh weight (Mattila et al., 1994). Cultivated mushrooms do not contain high amounts of vitamin D_2 since they are grown in the dark, but UVB treated vitamin D_2 enhanced mushrooms are now commercially available.

44. Rich sources of vitamin D_3 include egg yolk (12.6 µg/504 IU per 100 g) and oily fish (5-16 µg/200-640 IU per 100 g) such as salmon, mackerel, herring and sardines. Animal products such as meat, fat, liver and kidney also contain vitamin D_3 (0.1-1.5 µg/4-60 IU per 100g). Vitamin D_3 in addition to 7-DHC has also been identified in the leaves of plant species belonging to the Solanaceae family (which includes vegetables such as potato, tomato and pepper). Wide variations have been reported in how much vitamin D_3 and 7-DHC the leaves of these plants contain. Vitamin D_3 has been reported to be present between <0.1-0.28 µg/g dry weight and 0.1- 42 µg/g fresh weight, whereas 7-DHC has been reported to be present between 2 -1.3 µg/g dry weight and 5-58 µg/g fresh weight. However, it is unknown if the edible portions of plants in this family also contain vitamin D_3 (SACN, 2016), but the COT considered it unlikely that the edible portions of the plants will contain a significant amount of vitamin D_3.

45. In the UK, foods such as fat spreads, breakfast cereals, dried and evaporated milk (SACN, 2016) and plant-based drinks can also be fortified with vitamin D_3 or D_2 on a voluntary basis. The following data on fortification levels of vitamin D were collected from UK supermarket websites. However, the nutritional information provided by the retailer did not specify if foods were fortified with vitamin D_2, D_3 or both.

46. The level of fortification of vitamin D in 20 examples of margarines and fat spreads ranged between 5-7.5 µg/100g (Sainsbury's, Tesco, 2020). For breakfast cereals, data collected from UK supermarket websites showed the level of fortification of vitamin D in 36 samples to range between 2.5-8.4µg per 100 g of breakfast cereals (Sainsbury's, 2020). Additionally, the level of vitamin D ranged between 0.15-4.6 µg/100g in 3 samples of dried milk and 26-29 µg/kg in 2 samples of evaporated (Sainsbury's, Tesco, 2021). Further fortification levels of vitamin D levels ranged between 0.75-1.8 µg/100g plant-based drinks (Sainsbury's, 2021).

Cow's milk and milk products

47. "In the UK, cows' milk is generally not a good source of vitamin D because it is not fortified, as it is in some other countries" (NHS, 2020). However, dried and evaporated milks are fortified with vitamin D on a voluntary basis (SACN, 2016). Data collected from UK supermarket websites showed the level of fortification of vitamin D to be between 0.15-4.6 µg per 100 g of in 3 samples dried milk, and 2.6-2. 9 µg per 100g in 2 samples of evaporated milk (Sainsbury's Tesco, 2020).

Supplements

48. Dietary vitamin D supplements contain either vitamin D_2 or D_3, they are synthesised commercially by UVB irradiation of 7-DHC (from sheep wool) and ergosterol (from fungi) respectively (Bikle, 2009). Vitamin D supplements can also be administered by intramuscular injection.

49. The dosage of vitamin D supplied by the supplements currently available on the market ranges from 4 -180 µg/day.

50. From late March/early April to the end of September, most people should be able to get all the vitamin D they need from sunlight on their skin and a balanced diet. During the autumn and winter, all adults (including pregnant and breastfeeding women) and children over four years old are advised to consider taking a daily vitamin D supplement (10 micrograms/400 IU) to protect bone and muscle health. Groups who are at risk of not obtaining enough vitamin D from sunlight exposure are advised to take a vitamin D supplement all year round. These groups include people with dark skin (such as those with African, African-Caribbean or South Asian backgrounds), those who spend most of their time indoors (for example, because of frailty or they are living in a care home) and those who cover most of their skin when outdoors (NHS, 2021).

Exposure assessment

Food

51. The following exposure assessments are based on consumption data from the NDNS (Bates *et al*., 2014, 2016; Roberts *et al*., 2018), it is important to note that the NDNS does not provide data for pregnant or lactating women. Therefore, data presented below is based on women of childbearing age (16-49 years) and consumption data may not entirely be representative of the maternal diet.

Exposure estimates from foods with naturally occurring vitamin D_2.

Mushrooms:

52. As noted in paragraph 39, wild mushrooms are a natural source of vitamin D_2. A search within the recipes database of the NDNS (Bates *et al*., 2014, 2016; Roberts *et al*., 2018) was conducted to retrieve mushrooms and recipes containing mushrooms which had been recorded in the survey.

53. The chronic consumption estimates of mushrooms are presented in Table A1 of Annex A. It is important to consider that these estimates are based on all mushrooms, as there is negligible consumption data on wild mushrooms in the NDNS (Bates *et al*., 2014, 2016; Roberts *et al*., 2018).

54. Exposure estimates of vitamin D_2 in mushrooms were calculated using chronic consumption data from Table A1 and, the minimum and maximum estimated vitamin D_2 levels for wild mushrooms which are 130 and 300 µg/kg respectively (SACN, 2016), these are given in Table A2 of Annex A.

Exposure estimates from foods with naturally occurring vitamin D_3.

Egg yolk:

55. Natural sources of Vitamin D_3 include egg yolk; chronic consumption estimates of egg yolk are presented in Table A3 of Annex A. It is important to note that whole egg consumption from the NDNS database was considered in order to ensure that all egg yolk consumers were included. On average, the egg yolk makes up 29.3% of the edible portion of a medium egg, and 28.7% of a large egg. The NDNS database does not specify the use of large or medium eggs so the figure was rounded to 29% for this paper (DH, 2012). The factor of 29% was then applied to whole eggs foods to give estimates for consumption specifically of egg yolks, and foods containing solely egg whites were removed from the assessment.

56. Exposure estimates of vitamin D_3 in egg yolk using chronic consumption data from Table A3 of Annex A and estimated vitamin D_3 levels of 126 µg/kg (SACN, 2016) are presented in Table A4 of Annex A.

Oily fish:

57. Additional sources of vitamin D_3 are oily fish such as salmon, mackerel, herring and sardines, for which chronic consumption data is presented in Table A5 of Annex A.

58. Exposure estimates of vitamin D_3 in oil fish using chronic consumption data from Table A5 of Annex A and minimum and maximum estimated vitamin D_3 levels of 50 and 160 µg/kg (SACN, 2016) respectively are presented in Table A6 of Annex A.

Animal meat and fat:

59. Further sources of vitamin D_3 are animal meat and animal fat. Consumption estimates of various types of animal meat and fat (chicken, beef, pork and turkey) are presented in Tables A7-10 Annex A. Consumption of animal meat and animal fat were considered together as animal fat is likely to be consumed alongside animal meat. Additionally, the number of consumers of animal fat alone would be very low.

60. Exposure estimates of vitamin D_3 in animal meat and animal fat using chronic consumption data from Table A7-10 of Annex A and minimum and maximum estimated vitamin D_3 levels of 1 and 15 µg/kg respectively (SACN, 2016) are presented in Table A11-14 of Annex A.

Animal offal:

61. Other sources of vitamin D_3 is animal liver and kidney. Consumption estimates of animal liver and kidney are based on overall animal offal consumption and are presented in Table A15 of Annex A. Consumption was based on all animal offal as liver and kidney were given as examples of offal that contain vitamin D_3 in the 2016 SACN report and other types of offal were not specified (SACN, 2016).

62. Exposure estimates of vitamin D_3 in animal liver and kidney using chronic consumption data from Table A15 of Annex A and minimum and maximum estimated vitamin D_3 levels of 1 and 15 µg/kg respectively (SACN, 2016) are presented in Table A16 of Annex A.

Exposure estimates from food voluntarily fortified with Vitamin D

63. As previously mentioned, the following foods are voluntarily fortified with vitamin D: margarines and fat spreads, breakfast cereals, dried and evaporated milk and plant-based drinks. Consumption estimates of these food products are presented in Table A17 of Annex A.

64. It is important to note that consumption estimates of plant-based drinks are based on cow's milk due to limited number of consumers of plant-based drinks in the NDNS. Additionally, the consumption estimates are based on consumption of cow's milk on its own, in breakfast cereals and hot beverages such as tea and coffee.

65. Exposure estimates of vitamin D in fortified foods using chronic consumption data from Table A17 of Annex A and various minimum and maximum estimated vitamin D levels are presented in Table A18 of Annex A.

66. Minimum and maximum estimated vitamin D levels for margarine and fat spreads were 50 and 75 µg/kg (Sainsbury's, Tesco, 2020) respectively. For breakfast cereals minimum and maximum estimated vitamin D levels were 25 and 84 µg/kg (Sainsbury's 2020). As for dried milk minimum and maximum estimated vitamin D levels were 1.5 and 46 µg/kg respectively, and for evaporated milk estimated vitamin D levels were 26 and 29 µg/kg. Additionally, plant-based drinks had minimum and maximum estimated vitamin D levels of 7.5 and 18 µg/kg respectively. More specifically soya, coconut and almond milk alternatives had vitamin D levels of 7.5 µg/kg and oat milk alternatives had minimum and maximum estimated vitamin D levels of 7.5 and 18 µg/kg respectively (Sainsbury's, Tesco, 2020).

67. As discussed in paragraph 33, the form of vitamin D that these foods were fortified with were not specified. However, their exposures will be compared to the TUL of 100 µg/day which is protective of both forms of vitamin D (D_2 and D_3).

Exposure estimates from supplements only

68. The most recent NDNS report has shown that between 2016 and 2019 20% of female respondents aged 19-64 years were vitamin D supplement takers (Bates et al., 2020).

69. Supplements aimed at non-pregnant adults supplied vitamin D in doses ranging from 4 to 180 µg/day. The supplements containing vitamin D that are aimed at pregnant and breast-feeding women contain no more than 10 µg/day of vitamin D. For women attempting conception supplements contain no more than 20 µg/day of vitamin D (PAGB, OTC,2020; Vitabiotics, 2020; iherb, 2020). However, it is important to note that many individuals may be unaware of their pregnancy and may consume doses higher than those intended for pregnant women.

70. There are limited data on vitamin D supplement use in the UK. However, a 2018 food supplements consumer research report that surveyed 2081 participants (with 1063 being female) has reported that vitamin D is taken by 29% of regular supplement consumers and is “most popular amongst women (35% compared to 24% of men). The research report also noted one of the reasons for consumers to start taking supplements such as vitamin D, are seasonal triggers, such as the start of winter. Other reasons included “reaching a specific life stage was often the prompt for people to start taking a food supplement, for example women trying to get pregnant…or young adults leaving home and having to cook for themselves”. Further reasons were that “a bout of illness often resulted in people taking a food supplement, either to try to get better or to avoid becoming afflicted again” (FSA, 2018).

71. Due to the ongoing COVID-19 pandemic there has been increased interest in vitamin D due to studies reporting associations between vitamin D deficiency COVID-19 risk (Meltzer et al., 2020), and 25(OH)D levels and hospitalised COVID-19 patients (Hernández, 2021). These publicised research results may increase the consumption of vitamin D supplements by the population to levels higher than normal. It has been reported that vitamin D usage has risen 8% between October 2019 to 0ctober 2020. There has also “been a 20% increase in new product launches containing vitamin D from January to August 2020 compared of the whole of 2019” (Nutra Ingredients, 2020).

72. The current recommendation from the National Institute for Health and Care Excellence (NICE) and the NHS is to “not offer a vitamin D supplement to people solely to prevent COVID-19, except as part of clinical trial” and that “people should be encouraged to follow the existing UK government advice on vitamin D supplementation” (NICE, 2021; NHS, 2021). However, it was agreed that “the recommendations in this guideline on vitamin D supplements and COVID-19 prevention should be considered for an update as additional evidence becomes available” (NICE, 2021).

73. Mean and 97.5th percentile values of all vitamin D containing supplements are presented in Table 1. It is important to note that the calculated mean and 97.5th percentile values are based on the samples of vitamin D containing supplements and recommended doses and not on the consumption pattern. The mean and 97.5th percentile values are also based on a limited number of vitamin D containing supplements (presented in Table A1 of Annex A) and not all those that are currently available in the UK. Therefore, the values reported may likely be underestimates and a significant portion of the population may be exposed to higher doses if they consume multiple supplements containing vitamin D.

Table 1. Mean and 97.5th percentile exposure from vitamin D containing supplements.*

	(µg/person/day)*		**µg/kg bw/day***	
Vitamin D concentration	Mean	97.5th percentile	Mean**	97.5th percentile**
	17	162	0.22	2.1

* Rounded to 2 s.f
** Based on a body weight of 78.6 kg
** Mean and 97.5th percentile estimates are based on 48 vitamin D containing supplements

Estimated total vitamin D exposure from food sources (excluding supplements)

74. Estimated total exposure to vitamin D from food sources in women aged 16-49 years only, are presented in Table 2 below. These data have been summed from the consumer-based exposure estimates in tables A2, 4, 6, 11-14, 16 and 18 of Annex A. Exposure data from food sources containing both forms of vitamin D (D_2 and D_3) were summed together as their exposures will be compared to the TUL of 100 µg/day which is protective of both forms of vitamin D (D_2 and D_3).

Table 2. Estimated total vitamin D exposure from food sources (excluding supplements) in women aged 16-49 years.

Total vitamin D intake - (food sources)	**(µg/person/day)***		**µg/kg bw/day***	
	Mean	**97.5th percentile**	**Mean**	**97.5th percentile**
Minimum	6.5	22	0.094	0.34
Maximum	16	56	0.24	0.88

* Rounded to 2 s.f

75. Minimum vitamin D intake from food sources (excluding supplements) amongst women aged 16-49 years were 6.5 µg/day and 22 µg/day in mean and 97.5th percentile groups respectively. Alternatively, maximum vitamin D intake from food sources only were 16 and 56 µg/day in mean and 97.5th percentile groups respectively. However, it is important to note these maximum vales are likely to be an overestimate and it is unlikely that a consumer would reach a maximum dietary exposure level from their diet alone.

Estimated total vitamin D exposure from all dietary sources (including supplements):

76. Total exposure to vitamin D from all dietary sources (including supplements) in women aged 16-49 years are presented in Table 3 below. The exposure data from food sources in tables A2, 4, 6, 11-14, 16 and 18 of Annex A were summed with exposure data from dietary supplements (Table 19). Exposure data from food sources and supplements containing both forms of vitamin D (D_2 and D_3) were summed together as their exposures will be compared to the TUL of 100 µg/day, which is protective of both forms of vitamin D (D_2 and D_3).

Table 3. Estimated total vitamin D exposure from all dietary sources (including supplements) in women aged 16-49 years.

Total vitamin D intake - (all sources inc. supplements)	**(µg/person/day)***		**µg/kg bw/day***	
	Mean	**97.5th percentile**	**Mean**	**97.5th percentile**
Minimum	23	184	0.31	2.4
Maximum	33	220	0.46	2.9

* Rounded to 2 s.f

77. Minimum total vitamin D intake from all dietary sources (including supplements) amongst women aged 16-49 years were 23 and 184 µg/day in mean and 97.5th percentile groups respectively. Alternatively, maximum total vitamin D intake from all food sources were 33 and 220 µg/day in mean and 97.5th percentile groups respectively. However, as previously mentioned it is important to note the maximum dietary values used in this total exposure calculation are likely to be an overestimate, whilst the maximum supplement exposure values used in this total exposure calculation are likely to be an underestimate.

78. Table 4. shows comparisons of vitamin D exposure from different sources (food sources (excluding supplements), supplements only and food sources (including supplements)) and indicate that supplements are likely to be the biggest contributor to vitamin D exposure.

Table 4. Estimated vitamin D exposure from food sources, supplements and food and supplements in women aged 16-49 years.

	Food Sources (exc. Supplements)		**Supplements**		**Food sources (inc. supplements)**	
	Mean	97.5th percentile	Mean	97.5th percentile	Mean	97.5th percentile
Minimum (µg/person /day)	6.5	22	17	162	23	184
Maximum (µg/person /day)	16	56	17	162	33	220

* Rounded to 2 s.f

Risk characterisation

79. Exposure to UV radiation is unlikely to result in adverse serum 25(OH) levels even when consuming high dietary intakes of vitamin D due to the inbuilt mechanisms in the skin discussed in paragraph 38. Additionally, the excess pre-vitamin D_3 produced in the skin when it is exposed to UVB radiation are photodegraded into the following products: (several suprasterols and 5,6-trans-vitamin $D_{3)}$ that have no calcemic activity, so no matter how much sun exposure an individual receives vitamin D intoxication will not occur" (Wacker and Holick, 2013). Consequently, the possibility of vitamin D intoxication via UV exposure has not been considered further.

80. All mean and 97.5th percentile exposures from food sources (excluding supplements) for women of childbearing age (i.e., 16-49 years) are within the TUL of 100 µg/day (EFSA, 2012) and are therefore not of toxicological concern.

81. When considering vitamin D containing supplements, the majority of supplements aimed at non-pregnant adults are supplied in doses ranging from 4 to 180 µg/day, most of which do not exceed the TUL of 100 µg/day. However, the

highest dose vitamin D containing supplement; Zahler, Vitamin D3, exceeded the TUL by approximately 2-fold. Consumption of this supplement, and supplements containing vitamin D greater than 100 µg/day, may increase risk of hypercalcemia and hypercalciuria in women attempting conception, pregnant and lactating women. Despite the possible exceedances with some supplements, it is important to note that (COT, 2014) have previously concluded that occasional or short-term consumption of single and/or occasional "doses of 7500 µg at intervals of 3 months or longer would not be expected to cause adverse effects in" male and female "adults". However, this dose level is based on the adverse effects or lack of adverse effects reported in elderly subjects in a randomised clinical trial and is not specific to pregnant adults. Additionally, the COT agreed that "there is greater uncertainty about the effects of larger doses…even if only given infrequently" (COT, 2014). However, sustained consumption could be of toxicological concern, especially as supplements tend to use vitamin D in the form of D_3, due to its reported higher bioavailability than D_2 (Tripkovic et al., 2012).

82. Supplements that are aimed at and pregnant and breast-feeding women do not exceed the TUL for vitamin D of 100 µg/day (EFSA, 2012), and therefore exposure to vitamin D in these supplements alone are unlikely to be of toxicological concern to women attempting conception, pregnant and breast-feeding women. However, women who are unaware of their pregnancy and are consuming regular vitamin D supplements may have intakes closer to the TUL.

83. Estimates from all dietary sources (including supplements) amongst women of childbearing age (i.e.,16-49 years) mean total intakes were within the TUL of 100 µg/day (EFSA, 2012). Estimated intakes at the 97.5th percentile groups exceeded the TUL up to approximately 2-fold. It is important to note that the levels of exposure in the 97.5th percentile groups are more likely to reflect consumption of higher strength supplements that are greater than the current recommended amount of 10 µg/day. However, risk of hypercalcemia and hypercalciuria in women attempting conception, pregnant and lactating women cannot be excluded at the highest levels of intake.

84. Ultimately it is important to highlight that there is some uncertainty with the estimated intakes discussed above. The NDNS excludes data from pregnant and lactating women, so women of child-bearing age (16-49 years) have been used as a proxy for these consumer groups.

Conclusions

85. Women attempting conception, pregnant and lactating women who do not take supplements, and whose only exposure to vitamin D are from food sources (excluding supplements), are very unlikely to be at risk of adverse health effects such as hypercalcemia and hypercalciuria, as exposure estimates for women in this category are within the TUL of 100 µg/day.

86. When considering estimates from all dietary sources (including supplements) for woman of childbearing age, mean total intakes were within the TUL of 100 µg/day. Whereas, estimated 97.5th percentile intakes exceeded the TUL by up to 2-

fold. However, this is likely to only be of concern if exposures at the 97.5th percentile were sustained long term. Furthermore, these 97.5th percentile exposures are below the NOAEL of 250 µg/day which was identified in adults and was used to establish the TUL of 100 µg/day (EFSA, 2012). However, the risk of hypercalcemia and hypercalciuria in women attempting conception, pregnant and lactating women cannot be completely excluded, especially in a few sensitive individuals who may have loss of function mutations.

87. It is important to note that the contribution of vitamin D from the diet is much lower than from supplements, and the levels of exposure in the 97.5th percentile groups are more likely to reflect consumption of higher strength supplements that are greater than the current recommended amount of 10 µg/day. The major risk of excess vitamin D exposure is in relation to supplement consumption rather than consumption of vitamin D containing foods. Also, the consumption of supplements reported is likely to be an underestimate as it based on a limited number of supplements available in the UK, and a portion of the population may be exposed to vitamin D doses from more than one supplement.

88. Furthermore, sustained excessive vitamin D intake (i.e. >100 µg/day) mainly from supplements may be of concern due to many of these supplements using vitamin D in the form of D_3, which has a higher bioavailability than D_2.

89. Neither (SACN, 2016) or COT (2014) have identified a threshold for toxic symptoms but have previously agreed that occasional or short-term consumption of single and/or occasional “doses of 7500 µg at intervals of 3 months or longer would not be expected to cause adverse effects in” male and female “adults”. Although, this dose level is based on the adverse effects or lack of adverse effects reported in elderly subjects in a randomised clinical trial and is not specific to pregnant women.

90. Exposure from UV radiation is unlikely to result in vitamin D toxicity even when also consuming high dietary intakes, due to the inbuilt mechanisms in the skin. Further to this consumption from vitamin D containing supplements alone is sufficient to result in exceedance of the TUL. However, the diet alone without consumption of vitamin D containing supplements is unlikely to be a cause of concern, and consumption of both dietary sources of vitamin D and higher strength vitamin D supplements are likely to result in exposure levels greater than the TUL.

Secretariat
October 2021

Abbreviations

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
7-DHC	7-dehydroxycholesterol
$24,25(OH)_2D)$	24,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
COT	The Committee on Toxicity
CYP 2R1	Cytochrome P450 2R1
CYP 24A1	Cytochrome P450 24A1
CYP 27B1	Cytochrome P450 27B1
DBP	Vitamin D Binding Protein
DH	Department of Health
EFSA	The European Food Safety Authority
EVM	Expert group on Vitamins and Minerals
HBGV	Health Based Guidance Value
IU	International Units
Kg	Kilograms
NDNS	National Diet and Nutrition Survey
n	Number of samples
NHS	National Health Service
RCT	
RNI	Reference Nutrient Intake
SACN	Scientific Advisory Committee on Nutrition
TUL	Tolerable Upper Limit
µg	Micrograms
UK	United Kingdom
UVB	Ultraviolet B

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The data presented in the tables below are based on consumers of foods reported in NDNS (Bates et al., 2014, 2016; 2018)

Table A1. Estimated chronic consumption of mushrooms in women aged 16-49 years ()**

Number of consumers	(g/person/day)*		g/kg bw/day*		Respondents in population
	Mean	**97.5th percentile**	**Mean**	**97.5th percentile**	
871	11	49	0.16	0.70	1874

* Rounded to 2 s.f
**Based on all mushrooms in the NDNS database not just wild mushrooms

Table A2. Estimated chronic exposure of vitamin D_2 in mushrooms in women aged 16-49 years ()**

	(µg/person/day)*		µg/kg bw/day*	
Vitamin D concentration (µg/kg)	**Mean**	**97.5th percentile**	**Mean**	**97.5th percentile**
Minimum:130	1.5	6.4	0.021	0.091
Maximum: 300	3.4	15	0.049	0.21

* Rounded to 2 s.f
**Based on all mushrooms in the NDNS database not just wild mushrooms

Table A3. Estimated chronic consumption data of egg yolk in women aged 16-49 years ()**

Number of consumers	(g/person/day)*		g/kg bw/day*		Respondents in population
	Mean	97.5th percentile	Mean	97.5th percentile	
903	8.5	25	0.13	0.38	1874

* Rounded to 2 s.f
**Assumption: Average egg contains 29% egg yolk

Table A4. Estimated chronic exposure of vitamin D_3 in egg yolk in women aged 16-49 years ()**

Vitamin D concentration (µg/kg)	(µg/person/day)*		µg/kg bw/day*	
	Mean	97.5th percentile	Mean	97.5th percentile
126	1.1	3.2	0.016	0.048

* Rounded to 2 s.f
**Assumption: Average egg contains 29% egg yolk

Table A5. Estimated chronic consumption data of oily fish in women aged 16-49 years ()**

Number of consumers	(g/person/day)*		g/kg bw/day*		Respondents in population
	Mean	97.5th percentile	Mean	97.5th percentile	
311	25	70	0.38	1.3	1874

* Rounded to 2 s.f
**Based on salmon, mackerel, herring and sardines

Table A6. Estimated chronic exposure of vitamin D_3 in oily fish (salmon, mackerel, herring and sardines) in women aged 16-49 years ()**

	(µg/person/day)*		**µg/kg bw/day***	
Vitamin D concentration (µg/kg)	**Mean**	**97.5th percentile**	**Mean**	**97.5th percentile**
Minimum:50	1.3	3.5	0.019	0.066
Maximum: 160	4.0	11	0.061	0.21

* Rounded to 2 s.f

** Based on salmon, mackerel, herring and sardines

Table A7. Estimated chronic consumption of chicken and chicken fat in women aged 16-49 years ()**

	(g/person/day)*		**g/kg bw/day***		
Number of consumers	**Mean**	**97.5th percentile**	**Mean**	**97.5th percentile**	**Respondents in population**
1076	34	98	0.50	1.4	1874

* Rounded to 2 s.f

** Chicken and chicken fat have been considered together.

Table A8. Estimated chronic consumption of beef and beef fat in women aged 16-49 years ()**

	(g/person/day)*		**g/kg bw/day***		
Number of consumers	**Mean**	**97.5th percentile**	**Mean**	**97.5th percentile**	**Respondents in population**
1189	26	82	0.38	1.2	1874

* Rounded to 2 s.f

** Beef and beef fat have been considered together.

Table A9. Estimated chronic consumption of pork and pork fat in women aged 16-49 years ()**

Number of consumers	(g/person/day)*		g/kg bw/day*		Respondents in population
	Mean	**97.5th percentile**	**Mean**	**97.5th percentile**	
1110	23	80	0.33	1.3	1874

* Rounded to 2 s.f
** Pork and pork fat have been considered together.

Table A10. Estimated chronic consumption of turkey and turkey fat in women aged 16-49 years (Bates et al. ()**

Number of consumers	(g/person/day)*		g/kg bw/day*		Respondents in population
	Mean	**97.5th percentile**	**Mean**	**97.5th percentile**	
170	26	93	0.39	1.4	1874

* Rounded to 2 s.f
** Turkey and turkey fat have been considered together

Table A11. Estimated chronic exposure of vitamin D_3 in chicken and chicken fat in women aged 16-49 year)**

	(µg/person/day)*		µg/kg bw/day*	
Vitamin D concentration (µg/kg)	**Mean**	**97.5th percentile**	**Mean**	**97.5th percentile**
Minimum:1	0.034	0.096	0.00050	0.0014
Maximum: 15	0.51	1.5	0.0074	0.021

* Rounded to 2 s.f
** Chicken and chicken fat have been considered together.

Table A12: Estimated chronic exposure of vitamin D_3 in pork and pork fat in women aged 16-49 years ()**

	(µg/person/day)*		**µg/kg bw/day***	
Vitamin D concentration (µg/kg)	**Mean**	**97.5th percentile**	**Mean**	**97.5th percentile**
Minimum:1	0.023	0.080	0.00033	0.0013
Maximum: 15	0.34	1.2	0.0049	0.019

*Rounded to 2 s.f
** Pork and pork fat have been considered together.

Table A13: Estimated chronic exposure of vitamin D_3 in beef and beef fat in women aged 16-49 years ()**

	(µg/person/day)*		**µg/kg bw/day***	
Vitamin D concentration (µg/kg)	**Mean**	**97.5th percentile**	**Mean**	**97.5th percentile**
Minimum:1	0.026	0.082	0.00038	0.0012
Maximum: 15	0.39	1.2	0.0056	0.018

* Rounded to 2 s.f
** Beef and beef fat have been considered together.

Table A14: Estimated chronic exposure of vitamin D_3 in turkey and turkey fat in women aged 16-49 years ()**

	(µg/person/day)*		**µg/kg bw/day***	
Vitamin D concentration (µg/kg)	**Mean**	**97.5th percentile**	**Mean**	**97.5th percentile**
Minimum:1	0.026	0.093	0.00039	0.0014
Maximum: 15	0.39	1.4	0.0059	0.022

* Rounded to 2 s.f
** Turkey and turkey fat have been considered together.

Table A15. Estimated chronic consumption of animal liver and kidney in women aged 16-49 years ()**

Number of consumers	(g/person/day)*		g/kg bw/day*		Respondents in population
	Mean	**97.5th percentile**	**Mean**	**97.5th percentile**	
107	13	37	0.19	0.56	1874

*Rounded to 2 s.f
** Based on all animal offal

Table A16. Estimated chronic exposure of vitamin D_3 in animal liver and kidney in women aged 16-49 years ()**

	(µg/person/day)*		µg/kg bw/day*	
Vitamin D concentration (µg/kg)	**Mean**	**97.5th percentile**	**Mean**	**97.5th percentile**
Minimum:1	0.013	0.037	0.00019	0.00056
Maximum: 15	0.19	0.56	0.0028	0.0084

* Rounded to 2 s.f
**Based on all animal offal

Table A17. Estimated chronic consumption of voluntarily fortified foods in women aged 16-49 years ()

	(g/person/day) *		**g/kg bw/day***		**Respondents in population**
	Margarine and fat spreads				
Number of consumers	**Mean**	**97.5th percentile**	**Mean**	**97.5th percentile**	
1096	9.0	28	0.13	0.42	
	Breakfast cereals				
923	27	120	0.40	1.8	
	Dried milk				1874
1221	2.9	11	0.043	0.18	
	Evaporated milk				
16	8.8	33	0.12	0.47	
	Plant-based drinks				
1680	140	440	2.2	6.8	

*Rounded to 2 s.f

Table A18. Estimated chronic exposure of vitamin D in fortified foods (margarine and fat spreads, breakfast cereals and dried and evaporated milk and plant-based drinks) in women aged 16-49 years ()**

	(µg/person/day)*		**µg/kg bw/day***	
Vitamin D concentration (µg/kg)	**Mean**	**97.5th percentile**	**Mean**	**97.5th percentile**
	Margarine and fat spreads			
Minimum: 50	0.45	1.4	0.0066	0.021
Maximum: 75	0.67	2.1	0.0099	0.031
	Breakfast cereals			
Minimum: 25	0.66	3.0	0.010	0.044
Maximum: 84	2.2	10	0.033	0.15
	Dried milk			
Minimum: 1.5	0.0044	0.017	0.000065	0.00027
Maximum: 46	0.13	0.51	0.0020	0.0082
	Evaporated milk			
Minimum:26	0.23	0.87	0.0032	0.012
Maximum: 29	0.26	0.97	0.0036	0.014
	Plant-based drinks			
Minimum: 7.5	1.1	3.3	0.016	0.051
Maximum: 18	2.6	7.8	0.039	0.12

* Rounded to 2 s.f

** Estimated vitamin D levels were based on the following samples numbers:

Breakfast cereal n = 36; Dried milk n= 3; Evaporated milk n=2; Margarine and fat spreads n= 20; Plant-based drinks n= 27.