Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Statement on the potential effects of excess vitamin D intake during preconception, pregnancy and lactation

Introduction

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 to support their review. Therefore, 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, as part of this review.

Background

3. 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 available to humans via the diet. The other seco-steroid (vitamin D_3 or cholecalciferol) is synthesised in mammalian skin by the ultraviolet-B induced 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 42 and 45, 7-DHC is produced endogenously in the skin, but can also be found in the leaves of plant species belonging to the Solanaceae family (which includes vegetables such as potato, tomato and pepper). However, contribution of 7-DHC from the diet is likely to be very small as the leaves of these

plants are not commonly consumed because they contain toxic glycoalkaloids. Glycoalkaloids are present in all parts of the potato plant (i.e. tubers, roots, sprouts and leaves), with potato leaves containing higher concentrations of glycoalkaloids (i.e. solanine and chaconine) than the tubers. Tomato leaves and vines also contain glycoalkaloids (i.e. tomatine and dehydrotomatine), but they are not normally detectable in the fruit (Barceloux, 2009).

4. Since vitamin D can be synthesised endogenously (in the skin), is metabolised to the active form by the liver and kidney, and can regulate the transcription of vitamin D responsive genes and in turn 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

5. 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 immunoprotection 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).

6. When absorbed or released into the systemic circulation, both forms of vitamin D are transported to the liver by Vitamin D Binding Protein (DBP), where they are hydroxylated by 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.

7. 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, following facilitated uptake, to the hormonally active product 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) by CYP27B1. Both 25(OH)D and $1,25(OH)_2D$ are inactivated by CYP24A1-mediated hydroxylation.

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

9. 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 D_3 fall, prevent accumulation of toxic amounts of vitamin D_3 from cutaneous exposure alone" (Holick et al. 1980).

10. 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, the years of the survey (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 is unclear. This is due to many uncertainties such as season, time of day, amount of skin exposed, skin pigmentation and use of SPF sunscreen.

Status in pregnancy

11. 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 10 µg/day (400 IU/day) is inclusive of pregnant and lactating women.

12. 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).

13. However, a number of studies have reported uniquely high levels of $1,25(OH)_2D$ during pregnancy; the conversion of 25(OH)D to $1,25(OH)_2D$ during the first trimester (12 weeks of pregnancy) results in a doubling of $1,25(OH)_2D$ levels, and that levels continue to rise 2 to 3-fold from a non-pregnant adult baseline to over 700 pmol/L (0.7 nmol/L) (1 pmol/L = 0.001 nmol/L), 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) (1 ng/mL = 2.5 nmol/L) 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).

14. 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).

15. 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 the concentration of vitamin D in breast milk is higher than that of 25(OH)D or 1,25 $(OH)_2D$ (EFSA, 2016).

Excess vitamin D – human health studies and case reports

16. Hypervitaminosis D (excess vitamin D) can lead to hypercalcaemia (a total calcium concentration greater than 2.75 mmol/L), 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 (when urinary excretion of calcium exceeds 250 mg/day in women and 275-300 mg/day in men) (EVM, 2003).

17. High oral doses of vitamin D supplements have been shown to have toxic effects, such as hypercalcaemia, dehydration and tissue calcification (Vieth, 2006). 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 levels in cod-liver compounds and dried milk were halved in 1957. Following this there was a marked decrease in the number of infantile hypercalcaemia cases in the early 1960s (EVM, 2002).

18. Vomiting, nausea, constipation, and diarrhoea were reported as signs and symptoms of vitamin D overdosing in Danish infants who consumed a liquid vitamin D supplement that contained 150 µg (6,000 IU) of vitamin D_3 per drop instead of the indicated level of 2 µg (80 IU) per drop (Stafford, 2016). The recommended daily dose of this product was 5 drops therefore infants that consumed this supplement received 750 µg/day (30,000 IU) (Tetens et al., 2018) and exceeded the Danish Health and Safety Executive's recommended daily supplement intake of 8.5-10 µg (340-400 IU) for vitamin D for babies who do not consume 500 ml of infant formula per day (Mayor, 2016).

19. 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 25(OH)D levels, these were >150 nmol/L in 87/150 children that had consumed the supplement (Tetens et al., 2018).

20. Stoss (From the German stossen meaning "to push") 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 being treated (Çağlar and Çağlar, 2021).

21. 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 25,000-50,000 µg (1,000,000 – 2,000,000 IU). The duration of consumption of the fish oil supplements is unclear. The researchers determined that the minimum dose of vitamin D received causing vitamin D intoxication was 15,000 µg (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).

22. In other studies of stoss therapy using lower doses of vitamin D, there were no reports of vitamin D-related 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 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 treated either with 10 g 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 7,500 µg (300,000 IU) of vitamin D via injection. After treatment, mean serum 25(OH)D levels increased to 143.7 ± 77.7 nmol/L (57.5 ± 31.1 ng/mL) in those that received an ampoule dose via injection; 118 ± 62.2 nmol/L (47.2 ± 24.9 ng/mL) in those that received vitamin D capsules; and 98.9 ± 53.8 nmol/L (39.5 ± 21.5 ng/mL) in those that received fortified biscuits. Baseline 25(OH)D levels were reported only 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 (16.4 ng/mL), in those receiving ampoule dose via injection; 39.9 nmol/L (15.9 ng/mL) in those receiving vitamin D capsules; and 41.2 nmol/L(16.5 ng/mL) in those receiving fortified biscuits (Moslemi et al., 2018).

23. 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 2-18 years were administered vitamin D doses of 2,500 to 15,000 µg (100,000 – 600,000 IU). Serum 25(OH)D levels increased to 94.8 ± 41.0 nmol/L, 81.5 ± 24.6 nmol/L, 92.2 ± 36.5 nmol/L and 64.6 ± 20.0 nmol/L 1, 3, 16 and 12 months post treatment, respectively, and no evidence of vitamin D toxicity such as hypercalcaemia or hyperphosphatemia was observed. (Shepherd et al., 2013).

24. SACN (2016) reported that a number of cases of intoxication occurring as a result of high medicinal doses or excessive or mis-formulated supplement use were 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, some have cited 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, that the threshold for toxic effects is around 750 nmol/L 25(OH)D (Jones, 2008). It is important to note that a threshold for toxicity was not proposed by SACN or COT as the case reports provided only limited

information for risk assessment purposes as the doses consumed, where known, varied in amount and duration.

25. 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). Study results on hypercalcemia and hypercalciuria showed a significant dose dependent effect of vitamin D, with the percentage of participants that reported hypercalciuria as an adverse event 33% in those receiving 250 µg (10,000 IU) compared to 22% in those who received 100 µg (4,000 IU). Additionally, 17% of participants receiving 10 µg (400 IU) had hypercalciuria on at least one occasion over the study duration. For hypercalcemia, the figures for were 9%, 4% and 0%, respectively. The percentage of participants reporting renal dysfunction, nephrolithiasis and/or hepatic dysfunction was 2%, 1% and 3% respectively in both the group receiving 250 µg (10,000 IU) and that receiving 100 µg (4,000 IU). Figures for the 10 µg (400 IU) group were 1%, 0% and 5%, respectively. 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 and 4% in the 10 µg (400 IU) group. The study authors reached no conclusions on the possible negative effects of vitamin D on BMD because the measurements of volumetric BMD were in the opposite direction of the hypothesised effect. The results should be considered as hypothesis generating, requiring confirmation in further studies. However, it was noted that episodes of hypercalcemia and hypercalciuria were more common with increasing vitamin D dose (Burt et al., 2019).

26. 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 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 (Harwood et al., 2004).

27. 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 Jones (2008).

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

29. 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

30. There is currently no information 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, as such effects are outside the remit of this assessment. However, such supplement studies have not reported obvious adverse effects.

Pregnancy

31. Data on the effects of high levels of vitamin D intakes during pregnancy or lactation are limited (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.

32. A recent paper reported a case of a pregnant woman with disordered vitamin D metabolism due to compound loss of function CYP24A1 mutations who was supplemented with vitamin D_3 (cholecalciferol) 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 $1,25(OH)_2D$ 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) after delivery with loss of function CYP24A1 mutations (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).

33. Loss of function mutations 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 (Knabl et al., 2017).

Such polymorphisms are therefore more likely to contribute to effects associated with vitamin D deficiency rather than with an excess.

34. Excessive vitamin D intake during pregnancy can also result in risk of fetal hypercalcemia (Larquè et al., 2018), and hypercalcemia during pregnancy may be associated with increased risk of fetal and neonatal morbidity (Sato, 2008); the assertion in 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 a 25(OH)D level of 73 nmol/L, which was at the upper end of the reference range (50-75 nmol/L). The baby also had a total serum calcium level of 3.09 mmol/L, which was outside the reference range of 1.9-2.6 mmol/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 a total serum calcium level of 2.38 mmol/L which was within the reference range of 2.1-2.66 nmol/L.

35. Other potential adverse effects of vitamin D intake 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 (4,000 IU) (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 in 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). The levels that are considered deficient by SACN (2016) were based on the risk of developing rickets, and as discussed in paragraph 36, these levels would not be unusual in South Asian ethnicities in the UK during winter.

Lactation

36. Although there is very limited evidence for adverse effects relating to high 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

37. As noted above, in 2016, SACN set a reference nutrient intake (RNI) for vitamin D of 10 µg/day (400 IU/day) 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).

38. 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/day) supplementary vitamin D would not be expected to result in adverse health effects (EVM, 2003).

39. The European Food Safety Authority (EFSA) reviewed vitamin D in 2012 and established a Tolerable Upper Limit (TUL) of 100 µg (4,000 IU) vitamin D per day for adults and 25, 50 and 100 µg/day (1,000, 2,000 and 4,000 IU) vitamin D for infants and children aged up to 12 months, 1-10 years and 11-17 years, respectively. EFSA recognized that vitamin D_3 may raise 25(OH)D levels more than vitamin D_2, however, as the UL of 100 ug/day was supported by 2 studies both using vitamin D_2 and vitamin D_3, EFSA's TUL was considered 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).

40. 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

41. 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).

42. SACN has stated that "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

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

44. 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 (0.21 µg per 100 g fresh weight) since they are grown in the dark (Mattila et al., 1994). However, UVB treated vitamin D_2 enhanced mushrooms are now commercially available; fresh mushrooms that are exposed to UVB lamps can contain vitamin D_2 up to at least 10 µg per 100 g fresh weight (Cardwell et al., 2018). However, UK retailer websites state that UV treated mushrooms contain around 3-5 µg/100g fresh weight.

45. Rich dietary 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, as well as 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 at levels between <0.1-0.28 µg/g dry weight and 0.1- 42 µg/g

fresh weight, whereas 7-DHC has been reported at levels between 0.2 -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 represent a significant source of vitamin D_3.

46. In the UK, foods such as fat spreads, breakfast cereals, dried and evaporated milk (SACN, 2016) and plant-based drinks can 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.

47. The level of fortification of vitamin D in 20 examples of margarines and fat spreads ranged between 5.0-7.5 µg (200-300 IU)/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 2.5-8.4 µg (100-336 IU) per 100 g of breakfast cereals (Sainsbury's, 2020). Fortification levels of vitamin D levels in plant-based drinks ranged between 0.75-1.8 µg (30-72 IU) /100g plant-based drinks (Sainsbury's, 2021).

Cow's milk and milk products

48. The NHS states that "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), although such milk is now becoming available. However, dried and evaporated milks are often 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 (6-184 IU) per 100 g in 3 samples of dried milk, and 2.6-2.9 µg (104-116 IU) per 100g in 2 samples of evaporated milk (Sainsbury's Tesco, 2020).

Supplements

49. Dietary vitamin D supplements contain either vitamin D_2 or D_3, which 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.

50. The dosage of vitamin D supplied by the supplements currently available on the market ranges from 4 -180 µg/day (160-7,200 IU/day). It is important to note that the highest dose supplement available on the market provides 1,250 µg of vitamin D in one serving but the manufacturer recommended for this to be consumed only once a week, which would be equivalent to 180 µg/day.

51. From late March/early April to the end of September, most people should be able to obtain 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

52. 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 be entirely representative of the maternal diet. Evidence suggests that some foods and nutrients may be under-reported to a greater extent than others, and some may be overreported, but there is no information available on the level to which different foods and nutrients are misreported in the NDNS in this group.

Exposure estimates from foods with naturally occurring vitamin D_2

Mushrooms

53. As noted in paragraph 44, wild mushrooms are a natural source of vitamin D_2. However, UV-treated cultivated mushrooms can also contain high levels 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.

54. 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 types of mushrooms, as there is no separate consumption data on wild mushrooms; it is uncertain if any mushrooms reported in NDNS had been treated with UV (Bates et al., 2014, 2016; Roberts et al., 2018).

55. Exposure estimates of vitamin D_2 in wild mushrooms were calculated using consumption data from online sources (listed in Annex B), and the minimum and maximum estimated vitamin D_2 levels for wild mushrooms which are 130 and 300 µg/kg (5,200 and 12,000 IU/kg) respectively (SACN, 2016); these are provided in Table A2 of Annex A. As for cultivated mushrooms and UV treated mushrooms vitamin D_2 levels of 2.1 µg/kg (84 IU/kg) (Mattila et al., 1994) and 50 µg/kg (2,000 IU/kg) were used to calculate exposure estimates presented in Table A3 and A4 of Annex A respectively. It is important to note that UV-treated mushrooms tend to have a slightly higher retail price, though consumption estimates are assumed to be similar to those for cultivated mushrooms.

Exposure estimates from foods with naturally occurring vitamin D3

Egg yolk

56. Natural dietary sources of vitamin D_3 include egg yolk; chronic consumption estimates of egg yolk are presented in Table A5 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 excluded from the assessment.

57. Exposure estimates of vitamin D_3 from egg yolk using chronic consumption data from Table A3 of Annex A and estimated vitamin D_3 levels of 126 µg/kg (5,040 IU) (SACN, 2016) are presented in Table A6 of Annex A.

Oily fish

58. 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 A7 of Annex A.

59. Exposure estimates of vitamin D_3 from oily fish using chronic consumption data from Table A7 of Annex A and minimum and maximum estimated vitamin D_3 levels of 50 and 160 µg/kg (2,000 and 6,400 IU) (SACN, 2016), respectively are presented in Table A8 of Annex A.

Animal meat and fat

60. 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 A9-12 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.

61. Exposure estimates of vitamin D_3 in animal meat and animal fat using chronic consumption data from Table A9-12 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 A13-16 of Annex A.

Animal offal

62. Other sources of vitamin D_3 are animal liver and kidney. Consumption estimates for animal liver and kidney were 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 but other types of offal were not specified (SACN, 2016). The data are presented in Table A17 of Annex A.

63. Exposure estimates of vitamin D_3 from animal liver and kidney using chronic consumption data from Table A17 of Annex A and minimum and maximum estimated vitamin D_3 levels of 1 and 15 µg/kg (40 and 600 IU/kg), respectively (SACN, 2016) are presented in Table A18 of Annex A.

Exposure estimates from food voluntarily fortified with Vitamin D

64. 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 A19 of Annex A.

65. 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.

66. Exposure estimates of vitamin D from fortified foods using chronic consumption data from Table A19 of Annex A and various minimum and maximum estimated vitamin D levels are presented in Table A20 of Annex A.

67. Minimum and maximum estimated vitamin D levels for margarine and fat spreads were 50 and 75 µg/kg (2,000-3,000 IU) (Sainsbury's, Tesco, 2020) respectively. For breakfast cereals minimum and maximum estimated vitamin D levels were 25 and 84 µg/kg (1,000 and 3,360 IU) (Sainsbury's 2020). For dried milk minimum and maximum estimated vitamin D levels were 1.5 and 46 µg/kg (60 and 1,840 IU) respectively, and for evaporated milk estimated vitamin D levels were 26 and 29 µg/kg. Plant-based drinks had minimum and maximum estimated vitamin D levels of 7.5 and 18 µg/kg (300-720 IU), respectively. More specifically soya, coconut and almond milk alternatives had vitamin D levels of 7.5 µg/kg (300 IU) and oat milk alternatives had minimum and maximum estimated vitamin D levels of 7.5 and 18 µg/kg (300-720 IU), respectively (Sainsbury's, Tesco, 2020).

68. As discussed in paragraph 46, the form of vitamin D with which these foods were fortified was not specified. However, the respective exposures were compared to the TUL of 100 µg/day (4,000 IU/day), which is protective of both forms of vitamin D (D_2 and D_3).

Exposure estimates from supplements only

69. 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).

70. Supplements aimed at non-pregnant adults supplied vitamin D in doses ranging from 4 to 180 µg/day (160-7,200 IU/day). The supplements containing vitamin D that are aimed at pregnant and breast-feeding women contain no more than 10 µg/day (400 IU/day) of vitamin D. For women attempting conception supplements contain no more than 20 µg/day (800 IU/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 at the time, and may consume doses higher than those intended for pregnant women.

71. 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 (FSA, 2018). This aligns with NHS advice to “consider taking a daily supplement containing 10 µg of vitamin D during the autumn and winter” (NHS, 2021). 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).

72. In a prospective cohort study carried out with pregnant women in the North of Scotland where sunlight exposure is low (latitude 57°N), it was found that in the 21% of participants taking vitamin D supplements, the greatest influence on maternal and cord 25(OH)D levels was the season of birth ($P < 0{\cdot}001$). Amongst the participants consuming vitamin D supplements, the median intake was 5 µg (Haggarty, 2013).

73. Due to the ongoing COVID-19 pandemic there has been increased interest in vitamin D due to studies reporting associations between vitamin D deficiency and COVID-19 risk (Meltzer et al., 2020), and lower 25(OH)D levels and hospitalisation of 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 increased by 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 to the whole of 2019” (Nutra Ingredients, 2020).

74. 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 a 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).

75. 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 1) and not all those that are currently available in the UK. Therefore, the values reported are likely to 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.*

Vitamin D exposure	**(µg/person/day)*** Mean 17	**µg/kg bw/day*** Mean** 0.22
97.5th percentile	162	n/a
97.5th percentile**	n/a	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)

76. Estimated total exposure to vitamin D from only food sources in women aged 16-49 years, are presented in Table 2 below. These data have been summed from the consumer-based exposure estimates in tables A3, A6, A8, A13-16, A18 and A20 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 (4,000 IU) 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 exposure - (food sources)	**(µg/person/day)* Mean**	**97.5th percentile**	**µg/kg bw/day* Mean**	**97.5th percentile**
Minimum	5	16	0.073	0.25

Maximum	13	42	0.19	0.67

* Rounded to 2 s.f.
** Cultivated mushrooms were the only type of mushroom included when estimating total exposure from food sources, as they are the most commonly consumed type.

77. Minimum vitamin D intakes from food sources (excluding supplements) amongst women aged 16-49 years were 5 µg/day and 16 µg/day in mean and 97.5th percentile groups, respectively. Maximum vitamin D intakes from food sources only were 13 and 42 µg/day in mean and 97.5th percentile groups, respectively. However, it is important to note that these maximum vales are likely to be an overestimate and it is unlikely that a consumer would exceed the TUL of 100 µg/day from their diet alone.

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

78. 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 A3, A5, A8, A13-16, 18 and 20 of Annex A were summed with exposure data from dietary supplements (Table 1). 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 exposure - (all sources inc. supplements)	**(µg/person/day)* Mean**	**97.5th percentile**	**µg/kg bw/day* Mean**	**97.5th percentile**
Minimum	22	180	0.29	2.3
Maximum	30	200	0.41	2.7

* Rounded to 2 s.f.

79. Minimum total vitamin D intakes from all dietary sources (including supplements) amongst women aged 16-49 years were 22 and 180 µg/day in mean and 97.5th percentile groups, respectively. Maximum total vitamin D intakes from all food sources were 30 and 200 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 overestimates, whilst the maximum supplement exposure values used in this total exposure calculation are likely to be underestimates.

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

Table 4. Summary of estimated vitamin D exposures from food sources (excluding supplements), supplements and food sources (including supplements) in women aged 16-49 years.

Vitamin D exposure	**Food Sources (exc. Supplements) * Mean**	**97.5th percentile**	**Supplements* Mean**	**97.5th percentile**	**Food sources (inc. supplements)* Mean**	**97.5th percentile**
Minimum (µg/person /day)	5	16	17	162	22	180
Maximum (µg/person /day)	13	42	17	162	30	200

* Rounded to 2 s.f.

Risk characterisation

81. 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 42. Additionally, the excess pre-vitamin D_3 produced in the skin when it is exposed to UVA and UVB radiation is photodegraded into several suprasterols and 5,6-trans-vitamin D_3, which have no calcemic activity, so “no matter how much sun a human is exposed to intoxication will not occur because any excess previtamin D_3 and vitamin D_3 is photodegraded into products that have no calcemic activity” (Wacker and Holick, 2013). Consequently, the possibility of vitamin D intoxication via UV exposure has not been considered further.

82. 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.

83. 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 result in exceedances of the TUL of 100 µg/day. However, the highest dose vitamin D containing supplement results in an

exceedance of the TUL by approximately 2-fold. Consumption of this supplement, and supplements containing vitamin D greater than 100 µg/day, may increase the 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 single or occasional "doses of 7500 µg at intervals of 3 months or longer would not be expected to cause adverse effects in adults". 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 the more potent D_3, due to its reported higher bioavailability than D_2 (Tripkovic et al., 2012).

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

85. Considering exposure from all dietary sources (including supplements) amongst women of childbearing age (i.e.,16-49 years), mean total intakes were estimated to be within the TUL of 100 µg/day (EFSA, 2012). Groups with estimated intakes at the 97.5th percentile exceeded the TUL by 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, which contain greater than the current recommended amount of 10 µg/day for pregnant and breast-feeding women. However, risk of hypercalcemia and hypercalciuria in women attempting conception, pregnant and lactating women cannot be excluded at the highest levels of intake.

86. Ultimately it is important to highlight that there is some uncertainty with the estimated intakes discussed above. The NDNS excludes data for pregnant and lactating women, so women of child-bearing age (i.e. 16-49 years) have been used as a proxy for these consumer groups and there is little information on how their diets might differ.

Conclusions

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

88. When considering exposure estimates from all dietary sources (including supplements) for woman of childbearing age, mean total intakes were below the TUL of 100 µg/day. Whereas, estimated 97.5th percentile intakes exceeded the TUL by up to 2-fold. However, it is important to note that supplement use is the biggest driver of exposure from all dietary intakes at the 97.5th percentile, and is only likely to be of concern if exposures at the 97.5th percentile were sustained long term. 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 in CYP24A1, responsible for vitamin D inactivation.

89. 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, which contain greater than the current recommended amount of 10 µg/day for pregnant and breast-feeding women. Hence, the major risk of excess vitamin D exposure is in relation to supplement consumption rather than consumption of vitamin D containing foods. Also, the reported consumption of supplements 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 from more than one supplement.

90. Furthermore, sustained excessive vitamin D intake (i.e. >100 µg/day) mainly from supplements may be of particular concern because many of these supplements contain vitamin D in the form of the more potent D_3, which has a higher bioavailability than D_2.

91. Neither (SACN, 2016) nor COT (2014) have identified a threshold for toxic effects of excess vitamin D exposure but have previously agreed that single /or occasional “doses of 7500 µg at intervals of 3 months or longer would not be expected to cause adverse effects in adults”. 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.

92. Topical UV radiation is unable to increase systemic exposure to vitamin D sufficiently to cause toxicity, due to the inbuilt mechanisms for degradation of excess vitamin D in the skin. Dietary exposure to vitamin D from consumption of foods (excluding supplements), is very unlikely to result in sufficiently high levels of intake of the vitamin to be any cause for concern. Consumption of higher strength vitamin D supplements, either alone or in combination with dietary intake, may result in exposure levels that exceed the TUL and would therefore be of potential health concern. Consumption of lower strength supplements aimed at pregnant and breast-feeding women, either alone or in combination with dietary intake, is very unlikely to result in excessive exposure to vitamin D.

COT
Statement

01/22

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	Randomised Controlled Trial
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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Annex A

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

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

Number of consumer	**(g/person/day)* Mean**	**97.5th percentile**	**g/kg bw/day* Mean**	**97.5th percentile**	**Respondents in population**
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 wild mushrooms in women aged 16-49 years**

Vitamin D Concentration (µg/kg)	**Consumption of wild mushrooms per serving (g)***	**Exposure to vitamin D (µg/kg/bw day)^****
Minimum:130	25 -125	0.046 – 0.23
Maximum: 300	25 -125	0.11 – 0.53

*Rounded to 2 s.f.
**Based on online sources (recipes) (listed in Annex B).
^Average weight 70.3 kg sourced from NDNS.

Table A3. Estimated chronic exposure of vitamin D in cultivated mushrooms in women aged 16-49 years**

Vitamin D concentration (µg/kg)	**(µg/person/day)* Mean**	**97.5th percentile**	**µg/kg bw/day* Mean**	**97.5th percentile**
2.1	0.023	0.10	0.00034	0.0015

* Rounded to 2 s.f.
**Consumption figures sourced from NDNS years 1-8.

Table A4. Estimated chronic exposure of vitamin D in UV treated mushrooms* in women aged 16-49 years**[1].

Vitamin D concentration (µg/kg)^	**(µg/person/day)* Mean**	**97.5th percentile**	**µg/kg bw/day* Mean**	**97.5th percentile**
50	0.56	2.5	0.0081	0.035

* Rounded to 2 s.f.
** Consumption figures sourced from NDNS years 1-8 for cultivated mushrooms.
^ Concentration sourced from products from online supermarkets.

Table A5. Estimated chronic consumption data of egg yolk in women aged 16-49 years**

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

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

Table A6. Estimated chronic exposure of vitamin D_3 in egg yolk in women aged 16-49 years**

Vitamin D concentration (µg/kg)	**(µg/person/day)* Mean**	**97.5th percentile**	**µg/kg bw/day* 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 A7. Estimated chronic consumption data of oily fish in women aged 16-49 years**

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

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

Table A8. Estimated chronic exposure of vitamin D_3 in oily fish (salmon, mackerel, herring and sardines) in women aged 16-49 years**

Vitamin D concentration (µg/kg)	**(µg/person/day)* Mean**	**97.5th percentile**	**µg/kg bw/day* 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 A9. Estimated chronic consumption of chicken and chicken fat in women aged 16-49 years**

Number of consumers	**(g/person/day)* Mean**	**97.5th percentile**	**g/kg bw/day* 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 A10. Estimated chronic consumption of beef and beef fat in women aged 16-49 years**

Number of consumers	**(g/person/day)* Mean**	**97.5th percentile**	**g/kg bw/day* 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 A11. Estimated chronic consumption of pork and pork fat in women aged 16-49 years**

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

* Rounded to 2 s.f.

** Pork and pork fat have been considered together.

Table A12. Estimated chronic consumption of turkey and turkey fat in women aged 16-49 years**

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

* Rounded to 2 s.f.

** Turkey and turkey fat have been considered together.

Table A13. Estimated chronic exposure of vitamin D_3 in chicken and chicken fat in women aged 16-49 years**

Vitamin D concentration (µg/kg)	**(µg/person/day)* Mean**	**97.5th percentile**	**µg/kg bw/day* 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 A14: Estimated chronic exposure of vitamin D_3 in pork and pork fat in women aged 16-49 years**

Vitamin D concentration (µg/kg)	**(µg/person/day)* Mean**	**97.5th percentile**	**µg/kg bw/day* 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 A15: Estimated chronic exposure of vitamin D_3 in beef and beef fat in women aged 16-49 years**

Vitamin D concentration (µg/kg)	**(µg/person/day)* Mean**	**97.5th percentile**	**µg/kg bw/day* 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 A16: Estimated chronic exposure of vitamin D_3 in turkey and turkey fat in women aged 16-49 years**

Vitamin D concentration (µg/kg)	**(µg/person/day)* Mean**	**97.5th percentile**	**µg/kg bw/day* 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 A17. Estimated chronic consumption of animal liver and kidney in women aged 16-49 years**

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

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

Table A18. Estimated chronic exposure of vitamin D_3 in animal liver and kidney in women aged 16-49 years**

Vitamin D concentration (µg/kg)	**(µg/person/day)* Mean**	**97.5th percentile**	**µg/kg bw/day* 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 A19. Estimated chronic consumption of voluntarily fortified foods in women aged 16-49 years*

Respondents in population 1874

Type of food and number of consumers	**(g/person/day) * Mean**	**97.5th percentile**	**g/kg bw/day* Mean**	**97.5th percentile**
Margarine and fat spreads: 1096	9.0	28	0.13	0.42
Breakfast cereals: 92	27	120	0.40	1.8
Dried milk: 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 A20. Estimated chronic exposure of vitamin D in fortified foods (margarine and fat spreads, breakfast cereals and dried evaporated milk and plant-based drinks) in women aged 16-49 years**

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

Annex B

Online Sources (recipes)

Online sources for mushroom recipes described in paragraph 55 and Table A2 are listed below.

Mushroom and butternut squash dumplings recipe - BBC Food

Field mushroom soup recipe - BBC Food

Roasted sea bass with wild mushrooms recipe - BBC Food

Wild mushroom tartlets recipe | BBC Good Food

Fricassée of wild mushrooms recipe - Raymond Blanc OBE

Tagliatelle of wild mushrooms - The Happy Foodie

Wild mushroom and garlic rice recipe | delicious. magazine

Recipes | Vegetarian for Life

Creamy Vegan Gnocchi with wild mushrooms | The Veg Space

Beef, Baby Broccoli and Wild Mushrooms - SpiceYourCooking.com

Wild Mushroom Risotto - James Martin Chef

Wild Mushroom & Camembert Puff Parcels Recipe | Jus-Rol

Quail eggs with wild mushrooms - soft boiled quail eggs with wild mushroom and truffle oil (london-unattached.com)

Chicken supremes with wild mushroom and tarragon sauce recipe | delicious. Magazine

Spinach, wild mushroom and gruyere pancakes