TOX/2021/20

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. First 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].The Committee noted that further information on exposure to sunlight which is the main contributor to vitamin D formation and can greatly differ in winter and summer should be provided. It was also suggested that additional information on fetal hypercalcemia due to excess vitamin D intake and possible fetal morbidity should be discussed. Further suggestions included noting the incidence and effect of cytochrome P450 (CYP)24A1 and vitamin D receptor (VDR) polymorphisms on toxicity. However, discussions on VDR polymorphisms were not addressed in this statement in detail as their functional relevance in causing vitamin D excess is not clear[2]. They have been associated with increased susceptibility to conditions that are a result of low vitamin D such as rickets, hypocalcaemia (Malloy and Feldman, 2012)[3], preeclampsia, fetal growth restriction and diabetes in pregnancy (Knabi et al.,

[1] TOX/2021/08 is available on the COT website
[2] SACN (2016). SACN vitamin D and health report. https://www.gov.uk/government/publications/sacn-vitamin-d-and-health-report
[3] Malloy, P.J. and Feldman, D. (2011). The role of vitamin D receptor mutations in the development of alopecia. Molecular and cellular endocrinology, 347(1-2), pp.90-96.

2017)[4]. VDR polymorphisms may therefore be more likely to contribute to vitamin D deficiency rather than an excess. Members also agreed that an exposure assessment on the exposure to vitamin D from plant-based drinks would be required.[5]

4. The Committee are asked to consider the draft statement attached at Annex A which includes further information on exposure to sunlight in winter and summer, the incidence of CYP24A1 polymorphisms, fetal hypercalcemia and morbidity and exposure to vitamin D from plant-based drinks.

Questions for the Committee

Members are asked to consider the following questions:

a) Do members have any comments on the structure and content of the statement?

b) Does the Committee have any further comments?

c) Is the Committee content the functional relevance of the vitamin D receptor (VDR) causing excess vitamin D is not clear and does not need to be addressed in detail in this statement?

Secretariat

May 2021

[4] Knabl, J., Vattai, A., Ye, Y., Jueckstock, J., Hutter, S., Kainer, F., Mahner, S. and Jeschke, U., 2017. Role of placental VDR expression and function in common late pregnancy disorders. International journal of molecular sciences, 18(11), p.2340.

[5] COT Final minutes February 2021 is available on the COT website

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

First draft statement paper on the potential effects that excess vitamin D intake may have 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. Since vitamin D can be synthesised internally, it is often referred to in the literature as a hormone, rather than a vitamin.

Vitamin D function and status

3. 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 its 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 the these cellular processes (COT, 2014).

4. 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.

5. 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.

6. 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).

7. 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).

8. 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 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).

Status in pregnancy

9. There is a lack of data on what constitutes a healthy vitamin D status in pregnant women. 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.

10. Clinical trials with 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 suggest 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).

11. 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), 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 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).

12. 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).

13. 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

14. 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).

15. High oral doses of vitamin D supplements have been shown to have toxic effects, such as hypercalcaemia, dehydration and tissue calcification (Vieth, 2006). SACN, (2016) stated that "Evidence on vitamin D toxicity in humans is based on anecdotal case reports of acute accidental vitamin D_2 or D_3 intoxication resulting in plasma 25(OH)D concentrations of 710-1587 nmol/L". COT (2014) reported the majority of intoxication cases to be associated with serum 25(OH)D levels of as low as 300 nmol/L, but often exceeding 1000 nmol/L. The duration of consumption in these intoxication cases ranged from 4 days –10 years (COT, 2014). However, the threshold for toxic symptoms has been reported to be about 750 nmol/L (SACN, 2016).

16. 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).

17. 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).

[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.

Preconception

18. 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/d (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 trials have not resulted in obvious adverse effects being reported, though to what extent such effects would have been ascertained is unknown.

Pregnancy

19. Data on adverse effects 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/d (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.

20. A recent paper reported a case of a pregnant woman with disordered vitamin D metabolism due to a loss of function CYP24A1 mutations who were supplemented with Vitamin D 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 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).

21. 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.

22. 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 statement 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.

23. Other adverse effects of excessive vitamin D intake may include increases in blood pressure as reported in a randomised controlled trial. Healthy pregnant women in Bangladesh were administered high doses of vitamin D (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 was 26.7 nmol/L (Subramanian et al., 2020), which is lower than the level considered deficient by study researchers (i.e. <30 nmol/L of 25(OH)D) However, 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”, and the level noted in aforementioned study is above this (SACN, 2016).

Lactation

24. Although there is very limited evidence for adverse effects relating to vitamin D consumption during lactation, (Roth et al., 2018) found 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, as noted above, is lower than those considered deficient by study researchers.

Health based guidance values

25. 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).

26. 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).

27. 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).

28. The COT agreed that the EFSA TUL of 100 µg/d (4000 IU/d) 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

29. For most people, vitamin D_3 formation by exposure to UVB radiation is the main source of vitamin D. It is uncertain 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 had mean 25(OH)D levels of 70 nmol/L during winter. 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 65.4.5 nmol/L in summer and 47.2 nmol/L. 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).

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

Food

31. 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.

32. 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 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 5-58µg/g fresh weight. However, it is unknown if the edible portions of plants in this family also contain vitamin D_3 (SACN, 2016).

33. 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.

34. 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 100g 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

35. "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

36. 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.

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

38. 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

39. The following exposure assessments are based on consumption data from the NDNS (Bates et al., 2014, 2016, 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:

40. As noted in paragraph 31, wild mushrooms are a natural source of vitamin D_2. A search within the recipes database of the NDNS (Bates et al., 2014, 2016, 2018) was conducted to retrieve mushrooms and recipes containing mushrooms which had been recorded in the survey.

41. The chronic consumption estimates of mushrooms are presented in Table 1. 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).

Table 1. Estimated chronic consumption of mushrooms in women aged 16-49 years (Bates et al., 2014, 2016; 2018)**

	(g/person/day)*		**g/kg bw/day***		
Number of consumers	**Mean**	**97.5th percentile**	**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

42. Exposure estimates of vitamin D_2 in mushrooms were calculated using chronic consumption data from Table 1 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 2.

Table 2. Estimated chronic exposure of vitamin D_2 in mushrooms in women aged 16-49 years (Bates et al., 2014, 2016; 2018)**

	(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

Exposure estimates from foods with naturally occurring vitamin D_3.

Egg yolk:

43. Natural sources of Vitamin D_3 include egg yolk; chronic consumption estimates of egg yolk are presented in Table 3. 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.

Table 3. Estimated chronic consumption data of egg yolk in women aged 16-49 years (Bates et al., 2014, 2016; 2018)**

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

44. Exposure estimates of vitamin D_3 in egg yolk using chronic consumption data from Table 3 and estimated vitamin D_3 levels of 126 µg/kg (SACN, 2016) are presented in Table 4.

Table 4. Estimated chronic exposure of vitamin D_3 in egg yolk in women aged 16-49 years (Bates et al., 2014, 2016; 2018)**

	(µg/person/day)*		**µg/kg bw/day***	
Vitamin D concentration (µg/kg)	**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

Oily fish:
45. 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 5.

Table 5. Estimated chronic consumption data of oily fish in women aged 16-49 years (Bates et al., 2014, 2016; 2018)**

	(g/person/day)*		**g/kg bw/day***		
Number of consumers	**Mean**	**97.5th percentile**	**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

46. Exposure estimates of vitamin D_3 in oil fish using chronic consumption data from Table 5 and minimum and maximum estimated vitamin D_3 levels of 50 and 160 µg/kg (SACN, 2016) respectively are presented in Table 6.

Table 6. Estimated chronic exposure of vitamin D_3 in oily fish (salmon, mackerel, herring and sardines) in women aged 16-49 years (Bates et al., 2014, 2016; 2018)**

	(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

Animal meat and fat:

47. 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 7-10. 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.

Table 7. Estimated chronic consumption of chicken and chicken fat in women aged 16-49 years (Bates et al., 2014, 2016; 2018)**

	(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 8. Estimated chronic consumption of beef and beef fat in women aged 16-49 years (Bates et al., 2014, 2016; 2018)**

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

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

Table 9. Estimated chronic consumption of pork and pork fat in women aged 16-49 years (Bates et al., 2014, 2016; 2018)**

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 10. Estimated chronic consumption of turkey and turkey fat in women aged 16-49 years (Bates et al. (Bates et al., 2014, 2016; 2018)**

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.

48. Exposure estimates of vitamin D_3 in animal meat and animal fat using chronic consumption data from Table 7-10 and minimum and maximum estimated vitamin D_3 levels of 1 and 15 µg/kg respectively (SACN, 2016) are presented in Table 11-14.

Table 11. Estimated chronic exposure of vitamin D_3 in chicken and chicken fat in women aged 16-49 years (Bates et al., 2014, 2016, 2018)**

	(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 12: Estimated chronic exposure of vitamin D_3 in pork and pork fat in women aged 16-49 years (Bates et al., 2014, 2016, 2018)**

	(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 13: Estimated chronic exposure of vitamin D_3 in beef and beef fat in women aged 16-49 years (Bates et al., 2014, 2016, 2018)**

	(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 14: Estimated chronic exposure of vitamin D_3 in turkey and turkey fat in women aged 16-49 years (Bates et al., 2014, 2016, 2018)**

	(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.

Animal offal:

49. 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 15. 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).

Table 15. Estimated chronic consumption of animal liver and kidney in women aged 16-49 years (Bates et al., 2014, 2016; 2018)**

	(g/person/day)*		**g/kg bw/day***		
Number of consumers	**Mean**	**97.5th percentile**	**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

50. Exposure estimates of vitamin D_3 in animal liver and kidney using chronic consumption data from Table 15 and minimum and maximum estimated vitamin D_3 levels of 1 and 15 µg/kg respectively (SACN, 2016) are presented in Table 16.

Table 16. Estimated chronic exposure of vitamin D_3 in animal liver and kidney in women aged 16-49 years (Bates et al., 2014, 2016, 2018)**

	(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

Exposure estimates from food voluntarily fortified with Vitamin D

51. 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 17.

52. 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.

Table 17. Estimated chronic consumption of voluntarily fortified foods in women aged 16-49 years (Bates et al., 2014, 2016; 2018)

	(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

53. Exposure estimates of vitamin D in fortified foods using chronic consumption data from Table 17 and various minimum and maximum estimated vitamin D levels are presented in Table 18.

54. 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).

55. 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).

Table 18. 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 (Bates et al., 2014, 2016, 2018)**

	(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.

Exposure estimates from supplements only

56. 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).

57. Supplements aimed at non-pregnant adults supplied vitamin D in doses ranging from 5 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).

58. Mean and 97.5th percentile values of all vitamin D containing supplements are presented in Table 19. It is important to note that the calculated mean and 97.5th percentile values are based on a limited number of vitamin D containing supplements and not all those that are currently available in the UK.

Table 19. Mean and 97.5th percentile concentrations of 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	2.08

* Rounded to 2 s.f
** Mean and 97.5th percentile estimates are based on 48 vitamin D containing supplements

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

59. In the most recent NDNS survey, female respondents aged 19-64 years had mean and 97.5th percentile vitamin D intake of 2.6 and 7.7 µg/day respectively from all food sources (excluding dietary supplements) (Bates et al., 2020).

60. More specific estimated total exposure to vitamin D from food sources in women aged 16-49 years only are presented in Table 20 below. This data has been summed from the exposure estimates in tables 2, 4, 6, 11-14, 16 and 18. 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 20. Estimated total vitamin D exposure from food sources only (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

61. Minimum vitamin D intake from food sources only amongst women aged 16-49 years were 6.5µg/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):

62. In the most recent NDNS survey, female respondents aged 19-64 years had mean and 97.5th percentile vitamin D intake of 5.5 and 26.6 µg/day respectively from all food sources (including dietary supplements) (Bates et al., 2020).

63. More specific estimated total exposure to vitamin D from all dietary sources (including supplements) in women aged 16-49 years are presented in Table 21 below. The exposure data from food sources in tables 2, 4, 6, 11-14, 16 and 18 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 is protective of both forms of vitamin D (D_2 and D_3).

Table 21. 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	210	0.42	2.8

* Rounded to 2 s.f

64. Minimum total vitamin D intake from all dietary sources (including vitamin D) amongst women aged 16-49 years were 22 and 180 µg/day in mean and 97.5th percentile groups respectively. Alternatively, maximum total vitamin D intake from all food sources were 31 and 210 µg/day in mean and 97.5th percentile groups respectively.

Risk characterisation

65. The total vitamin D intake from all food sources (excluding supplements) amongst females aged 19-64 years in the most recent NDNS survey, were 2.6 and 7.7 µg/day for mean and 97.5th percentile values respectively (Bates et al., 2020). Both mean and 97.5th percentile values were well below the TUL of 100 µg/day (EFSA, 2012), and therefore do not indicate toxicological concern. However, these intake estimates include women outside of the ages of 16-49 years (i.e child-bearing age).

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

67. Majority of the vitamin D containing 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 dosed 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 occasional or short-term consumption of “doses of 7500 µg at intervals of 3 months or longer would not be expected to cause adverse effects in adults” (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 higher bioavailability than D_2 (Tripkovic et al., 2012).

68. Supplements that are aimed and pregnant and breast-feeding women do not exceed the TUL for vitamin D of 100µg/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.

69. The vitamin D intake from all dietary sources (including supplements) amongst females aged 19-64 years in the most recent NDNS survey were 5.5 and 26.6 µg/day for mean and 97.5th percentile groups respectively (Bates et al., 2020) which is below the TUL of 100 µg/day (EFSA, 2012). However, these intake estimates include women outside the ages of 16-49 years (i.e. child-bearing age).

70. When considering estimates from all dietary sources (including dietary supplements) for women of child-bearing age (i.e. 16-49 years) mean total intakes were within the TUL of 100 µg/day. Estimated intakes at the 97.5th percentiles exceeded the TUL approximately 2-fold and a risk of hypercalcemia and hypercalciuria in women attempting conception, pregnant and lactating women cannot be excluded.

Conclusions

71. Women attempting conception, pregnant and lactating women who do not take supplements, and whose only exposure to vitamin D is from food sources only, are unlikely to be at risk of adverse health effects such as hypercalcemia and hypercalciuria, as all exposure estimates for women in this category are below the TUL of 100 µg/day. However, effects to health cannot be excluded, especially in a few sensitive individuals who may have loss of function mutations.

72. When considering estimates from all dietary sources, including dietary supplements, for woman of childbearing age, mean total intakes were 23-33 µg/day which is within the TUL of 100 µg/day. Estimated intakes at the 97.5th percentiles were 184 – 210 µg/day which exceeds the TUL approximately 2-fold and a risk of hypercalcemia and hypercalciuria in women attempting conception, pregnant and lactating women cannot be completely excluded. The level 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 10µg/day.

73. 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.

74. Overall, current exposures to vitamin D from foods and supplements are unlikely to be of toxicological concern to the majority of women attempting conception, pregnant or lactating women.

Secretariat
May 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
RNI	Reference Nutrient Intake
SACN	Scientific Advisory Committee on Nutrition
TUL	Tolerable Upper Limit
µg	Micrograms
UK	United Kingdom
UVB	Ultraviolet B

References

Armas, L.A., Hollis, B.W. and Heaney, R.P., 2004. Vitamin D2 is much less effective than vitamin D3 in humans. *The Journal of Clinical Endocrinology & Metabolism*, *89*(11), pp.5387-5391.

Bao, W., Song, Y., Bertrand, K.A., Tobias, D.K., Olsen, S.F., Chavarro, J.E., Mills, J.L., Hu, F.B. and Zhang, C. (2018). Prepregnancy habitual intake of vitamin D from diet and supplements in relation to risk of gestational diabetes mellitus: A prospective cohort study. Journal of diabetes, 10(5), pp.373-379.

Bates, B.; Lennox, A.; Prentice, A.; Bates, C.; Page, P.; Nicholson, S.; Swan, G. (2014) National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009 – 2011/2012) Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/310995/NDNS_Y1_to_4_UK_report.pdf

Bates, B.; Cox, L.; Nicholson, S.; Page, P.; Prentice, A.; Steer, T.; Swan, G. (2016) National Diet and Nutrition Survey Results from Years 5 and 6 (combined) of the Rolling Programme (2012/2013 – 2013/2014) Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/551352/NDNS_Y5_6_UK_Main_Text.pdf

Bates, B.; Collins, D.; Jones, K.; Page, P.; Roberts, C.; Steer, T.; Swan, G.(2020) National Diet and Nutrition Survey Results from years 9, 10 and 11 (combined) of the Rolling Programme (2016/2017 to 2018/2019) Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/943114/NDNS_UK_Y9-11_report.pdf

Bikle D (2009) Nonclassic actions of vitamin D. J Clin Endocrinol Metab 94, 26-34.

Committee on toxicity of chemicals in food, consumer products and the environment (COT). (2014). Statement on adverse effects of high levels of vitamin D. https://webarchive.nationalarchives.gov.uk/20200808011447/https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2014/cot-statement-on-vitamin-d

Department of health (DH). (2012). Nutrient analysis of eggs Sampling Report. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/167974/Nutrient_analysis_of_eggs_Sampling_Report.pdf

Dinour, D., Davidovits, M., Aviner, S., Ganon, L., Michael, L., Modan-Moses, D., Vered, I., Bibi, H., Frishberg, Y. and Holtzman, E.J. (2015). Maternal and infantile hypercalcemia caused by vitamin-D-hydroxylase mutations and vitamin D intake. Pediatric Nephrology, 30(1), pp.145-152.

EFSA (2006). Scientific Committee on Food, EFSA panel on dietetic products, nutrition and allergies (NDA) Tolerable Upper Intake Levels for vitamins and minerals. http://www.efsa.europa.eu/en/ndatopics/docs/ndatolerableuil.pdf (Accessed August 2014)

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2012. Scientific opinion on the tolerable upper intake level of vitamin D. EFSA Journal, 10(7), p.2813. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2012.2813

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). (2016). Dietary reference values for vitamin D. EFSA Journal, 14(10), p.e04547. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2016.4547

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). (2018). Update of the Tolerable Upper Intake Level for Infants. EFSA Journal 16(8): 5365 https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5365

EVM (Expert Group on Vitamins and Minerals) (2003) Safe Upper Levels for Vitamins and Minerals, London: Food Standards Agency.

Greer, F.R., Hollis, B.W. and Napoli, J.L., 1984. High concentrations of vitamin D2 in human milk associated with pharmacologic doses of vitamin D2. The Journal of pediatrics (USA).

Heaney, R.P., 2008. Vitamin D in health and disease. Clinical Journal of the American Society of Nephrology, 3(5), pp.1535-1541.

Heaney, R.P., Armas, L.A., Shary, J.R., Bell, N.H., Binkley, N. and Hollis, B.W., 2008. 25-Hydroxylation of vitamin D3: relation to circulating vitamin D3 under various input conditions. The American journal of clinical nutrition, 87(6):1738-1742.

Heaney, R.P., Recker, R.R., Grote, J., Horst, R.L. and Armas, L.A., 2011. Vitamin D3 is more potent than vitamin D2 in humans. *The Journal of Clinical Endocrinology & Metabolism*, *96*(3), pp.E447-E452.

Holick MF, MacLaughlin JA & Doppelt SH (1981) Regulation of cutaneous previtamin D3 photosynthesis in man: skin pigment is not an essential regulator. Science 211: 590-593.

Hollis BW, Wagner CL. (2004). Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. Am J Clin Nutr. 80(6 Suppl):1752S-8S.

Hollis BW. (2005) Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr. 135(2):317-22.

Hollis, B.W., Johnson, D., Hulsey, T.C., Ebeling, M. and Wagner, C.L. (2011). Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. Journal of bone and mineral research, 26(10): pp.2341-2357.

iHerb (2020). https://uk.iherb.com/pr/Zahler-Vitamin-D3-50-000-IU-120-Capsules/76634?gclid=Cj0KCQiAw_H-BRD-ARIsALQE_2P31VL_JTVsViVAeCY0dE8Cj2epaBjzPKzb_VJqPRriliNWXigaDEkaAq3AEALw_wcB&gclsrc=aw.ds (Accessed 18th December 2020)

Jones G. (2008). Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr 88, 582S-586S.

Jones, G. (2016). CYP24A1 mutations and human diseas). Endocrine Abstracts. 41 S14.3. https://www.endocrine-abstracts.org/ea/0041/ea0041s14.3

Jukic, A.M.Z., Baird, D.D., Weinberg, C.R., Wilcox, A.J., McConnaughey, D.R. and Steiner, A.Z. (2019). Pre-conception 25-hydroxyvitamin D (25 (OH) D) and fecundability. Human Reproduction, 34(11), pp.2163-2172.

Kiely, M.E., Wagner, C.L. and Roth, D.E. (2020). Vitamin D in pregnancy: Where we are and where we should go. The Journal of steroid biochemistry and molecular biology, p.105669.

Kift R, Berry JL, Vail A, Durkin MT, Rhodes LE & Webb AR (2013). Lifestyle factors including less cutaneous sun exposure contribute to starkly lower vitamin D levels in U.K. South Asians compared with the white population. Br J Dermatol 169, 1272-1278.

Kovacs CS (2008) Vitamin D in pregnancy and lactation: maternal, fetal, and neonatal outcomes from human and animal studies. Am J Clin Nutr 88, 520S-528S.

Larqué, E., Morales, E., Leis, R. and Blanco-Carnero, J.E. (2018). Maternal and foetal health implications of vitamin D status during pregnancy. Annals of Nutrition and Metabolism, 72(3), pp.179-192.

MacDonald C, Upton, T, Hunt P, Philips I, Kaufmann M, Florkowski C, Soule S, Jones G. Vitamin D supplementation in pregnancy: A word of caution. Familial hypercalcaemia due to disordered vitamin D metabolism. Annals of Clinical Biochemistry, 57(2), pp. 186-191

Martin, N.D., Snodgrass, G.J. and Cohen, R.D. (1984). Idiopathic infantile hypercalcaemia--a continuing enigma. Archives of disease in childhood, 59(7), pp.605-613.

Mattila PH, Piironen VI, Uusi-Rauva EJ & Koivistoinen PE (1994) Vitamin D Contents in Edible Mushrooms. J Agricult Food Chem 42, 2449-2453.

Mumford, S.L., Garbose, R.A., Kim, K., Kissell, K., Kuhr, D.L., Omosigho, U.R., Perkins, N.J., Galai, N., Silver, R.M., Sjaarda, L.A. and Plowden, T.C., 2018. Association of preconception serum 25-hydroxyvitamin D concentrations with livebirth and pregnancy loss: a prospective cohort study [Abstract]. The Lancet Diabetes & Endocrinology, 6(9), pp.725-732.

NHS (2010). Consensus Vitamin D position Statement. https://www.nhs.uk/livewell/summerhealth/documents/concensus_statement%20_vitd_dec_2010.pdf

NHS (2021). https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-d/#:~:text=1%20microgram%20of%20vitamin%20D%20is%20equal%20to%2040%20IU.

Ovesen L, Brot C & Jakobsen J (2003). Food contents and biological activity of 25-hydroxyvitamin D: a vitamin D metabolite to be reckoned with? Ann Nutr Metab 47, 107-113.

Ota, K., Dambaeva, S., Han, A.R., Beaman, K., Gilman-Sachs, A. and Kwak-Kim, J., (2014). Vitamin D deficiency may be a risk factor for recurrent pregnancy losses by increasing cellular immunity and autoimmunity. Human reproduction, 29(2), pp.208-219.

PAGB, OTC directory (2020). https://www.otcdirectory.co.uk/list?title=Vitamin+D&single=0&page=1 (Accessed 17 December 2020)

Public Health England (2016). Government recommendations for energy and nutrients for males and females aged 1 – 18 years and 19+ years. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/618167/government_dietary_recommendations.pdf

Rey, E., Jacob, C.E., Koolian, M. and Morin, F., (2016). Hypercalcemia in pregnancy–a multifaceted challenge: case reports and literature review. *Clinical case reports*, *4*(10), p.1001.

Reynolds, A., O'Connell, S.M., Kenny, L.C. and Dempsey, E. (2017). Transient neonatal hypercalcaemia secondary to excess maternal vitamin D intake: too much of a good thing. Case Reports. pp.bcr-2016.

Roth, D.E., Morris, S.K., Zlotkin, S., Gernand, A.D., Ahmed, T., Shanta, S.S., Papp, E., Korsiak, J., Shi, J., Islam, M.M. and Jahan, I. (2018). Vitamin D supplementation in pregnancy and lactation and infant growth. New England Journal of Medicine, 379(6), pp.535-546.

Roberts, C.; Steer, T.; Maplethorpe, N.; Cox, L.; Meadows, S.; Page, P.; Nicholson, S.; Swan, G. (2018) National Diet and Nutrition Survey Results from Years 7 and 8 (combined) of the Rolling Programme (2014/2015 – 2015/2016) Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/699241/NDNS_results_years_7_and_8.pdf

Rudick B.J., Ingles S.A., Chung K., Stanczyk F.Z., Paulson R.J., Bendikson K.A.(2014) Influence of vitamin D levels on in vitro fertilization outcomes in donor-recipient cycles. Fertil. Steril.;101:447–452

SACN (2011) The influence of maternal, fetal and child nutrition on the development of chronic disease later in life: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/339325/SACN_Early_Life_Nutrition_Report.pdf

SACN (2016). SACN vitamin D and health report. https://www.gov.uk/government/publications/sacn-vitamin-d-and-health-report

SACN (2018) Feeding in the first year of life: https://www.gov.uk/government/publications/feeding-in-the-first-year-of-life-sacn-report

Sato, K., (2008). Hypercalcemia during pregnancy, puerperium, and lactation: review and a case report of hypercalcemic crisis after delivery due to excessive production of PTH-related protein (PTHrP) without malignancy (humoral hypercalcemia of pregnancy). *Endocrine journal*, pp.0804240109-0804240109.

Shah, A.D., Hsiao, E.C., O'Donnell, B., Salmeen, K., Nussbaum, R., Krebs, M., Baumgartner-Parzer, S., Kaufmann, M., Jones, G., Bikle, D.D. and Wang, Y. (2015). Maternal hypercalcemia due to failure of 1, 25-dihydroxyvitamin-D3 catabolism in a patient with CYP24A1 mutations. The Journal of Clinical Endocrinology & Metabolism, 100(8), pp.2832-2836.

Subramanian, A., Korsiak, J., Murphy, K.E., Al Mahmud, A., Roth, D.E. and Gernand, A.D. (2020). Effect of vitamin D supplementation during pregnancy on mid-to-late gestational blood pressure in a randomized controlled trial in Bangladesh. Journal of Hypertension.

Tripkovic, Laura, Helen Lambert, Kathryn Hart, Colin P. Smith, Giselda Bucca, Simon Penson, Gemma Chope et al. "Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis." *The American journal of clinical nutrition* 95, no. 6 (2012): 1357-1364.

Vieth R (1990). The mechanisms of vitamin D toxicity. Bone Miner 11: 267-272.

Vieth R (2006). Critique of the considerations for establishing the tolerable upper intake level for vitamin D: critical need for revision upwards. J Nutr 136: 1117-1122.

Vitabiotics (2020). https://www.vitabiotics.com/pages/ultra-supplements

Wagner CL, Hulsey TC, Fanning D, Ebeling M, Hollis BW.(2006). High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. Breastfeed Med. 1(2):59-70.

Wagner, C.L., Taylor, S.N., Johnson, D.D. and Hollis, B.W. (2012). The role of vitamin D in pregnancy and lactation: emerging concepts. Women's Health, 8(3): pp.323-340.

Webb AR, DeCosta BR & Holick MF (1989) Sunlight regulates the cutaneous production of vitamin D3 by causing its photodegradation. J Clin Endocrinol Metab. 68: 882-887.

Webb AR, Kift R, Berry JL & Rhodes LE (2011) The vitamin D debate: translating controlled experiments into reality for human sun exposure times. Photochem Photobiol 87, 741-745.