Introduction and Background

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This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

Introduction

1. In 2019, The Scientific Advisory Committee on Nutrition (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. A Statement on the potential effects of excess vitamin D intake during preconception, pregnancy and lactation was published by the COT in 2022. Following a discussion of the matter arising agenda item at the COT meeting of December 2022, the COT agreed that calcidiol should also be considered as an Annex to the Statement on the potential effects of excess vitamin D intake during preconception, pregnancy and lactation. This was on the basis that calcidiol is a more potent form of vitamin D2 and D3 and its availability on the market is increasing.

3. The toxicity and biological function of vitamin D and its status in pregnancy has been discussed in the Statement on the potential effects of excess vitamin D intake during preconception, pregnancy and lactation and therefore will not be discussed in detail in this paper.

Background

4. Calcidiol is a novel source of vitamin D3 (cholecalciferol), which is formed via chemical synthesis from cholestatrienol (ACNFP, 2024). Calcidiol is also known as calcidiol monohydrate, 25-hydroxycholecalciferol monohydrate (25(OH)D3 monohydrate) (EFSA, 2023), calcifediol or 25-hydroxyvitamin D (25(OH)D), with the latter two being the form used in supplementation (Biondi et al., 2017). Calcidiol is a synthetic form of 25(OH)D, which is an inactive precursor to the biologically active form of vitamin D known as 1,25-dihydroxyvitamin D (1,25 (OH)2D) and thus is commonly referred to as a pre-hormone (Vieth, 2020).

5. Calcidiol is more hydrophilic and has a shorter half-life than cholecalciferol (vitamin D3) whilst causing a rapid and sustained rise in serum 25(OH)D levels (Navarro-Valverde et al., 2016). This is due to differences in vitamin D3 absorption and hydroxylation in the liver, with calcidiol not requiring bile acids, which results in faster and more efficient absorption into systemic circulation (EFSA, 2022).

6. Calcidiol has been reported to be three to six times more potent than supplemental vitamin D3, meaning that lower doses of calcidiol are required to achieve the same serum 25(OH)D levels as vitamin D3 (Veith, 2020; Nishishinya, 2022). Other reports have showed 10 times more vitamin D3 than calcidiol is needed to increase serum 25(OH)D levels to equivalent serum concentrations (Stamp et al., 1977).

7. As Vitamin D and calcidiol are not equipotent there is no universal agreement by regulatory authorities on the conversion factor of calcidiol to

vitamin D3 in international units (IU) (Gázquez et al., 2022). However, conversion factors of 1.4- to 5-fold have been estimated by Cashnman et al., 2012 and Rossini et al., 2005) The European Commission (EC) asked the European Food Safety Authority (EFSA) to derive a conversion factor for calcidiol to vitamin D3 and the Panel on Nutrition, Novel Foods and Food Allergens (NDA) Panel derived a conversion factor of 5 that was established by the Panel on Additives and Products or Substances to convert calcidiol to vitamin D in animal Feed (EFSA, 2023a). EFSA also considered vitamin D equivalents (VDE) which is the expression of the “biological value of substances with vitamin D activity”. EFSA determined 1 ug of VDE to be equivalent to 0.4 µg of calcidiol, which in turn is equivalent to 40 IU.

8. However, after an updated exposure assessment in response to a request from EirGen Pharma Ltd to revise their previous opinion, EFSA proposed a conversion factor of 2.5 for the intake of calcidiol to VDE in December 2023, based on a systematic review of 10 randomised clinical trials (RCT). In these RCTs the effects of weekly and daily doses of calcidiol at 20 and 25 µg/day were compared to Vitamin D3 on serum 25(OH)D levels over a 6-week period. At doses of 20 µg/day the mean relative bioavailability of calcidiol was 2.02-fold higher than vitamin D3, whereas at 25 µg/day the mean relative bioavailability of calcidiol was 1.31-fold higher than vitamin D3. However, the mean relative bioavailability of calcidiol was 2.4-fold higher than vitamin D3 in EFSA’s meta-analysis including all available RCTs. In two RCTs that used reported doses of vitamin D3 at 60 µg/day the mean relative bioavailability of calcidiol was 2.11-fold higher than vitamin D3. (EFSA, 2023b).

9. The UK Advisory Committee for Novel Foods and Processes (ACNFP) also agreed with EFSA’s conversion factor of 2.5 (ACNFP, 2024). Based on the ACNFP review of a calcidiol application submitted by DSM Nutritional Products Ltd the FSA and FSS concluded calcidiol as “safe under the proposed conditions of use and does not pose a safety risk to human health” (ACNFP, 2024).