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SCIENTIFIC REPORT

Scientific and technical assistance to the evaluation of the safety of calcidiol monohydrate as a novel food

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Abstract

EFSA was asked by the European Commission to provide scientific assistance with respect to the EFSA adopted scientific opinion on 'Safety of calcidiol monohydrate produced by chemical synthesis as a novel food pursuant to Regulation (EU) 2015/2283', including its bioavailability as a metabolite of vitamin D_3 when added for nutritional purposes to food supplements. On 5 July 2023, EFSA adopted the 'Scientific opinion on the tolerable upper intake level for vitamin D, including the derivation of a conversion factor for calcidiol monohydrate'. This opinion concerns an updated exposure assessment for vitamin D and proposes a conversion factor for calcidiol monohydrate into vitamin D_3 of 2.5 for labelling purposes. In addition, in reference to the EFSA opinion on the safety of calcidiol monohydrate, the Commission had received a letter from the pharmaceutical company EirGen Pharma Ltd requesting a revision of this opinion based on new data concerning calcidiol. Based on the information and data considered in this scientific technical report, EFSA concludes that the novel food calcidiol monohydrate proposed for use in food supplements is a bioavailable source of the biologically active metabolite of vitamin D, i.e. 1,25-dihydroxyvitamin D, that a conversion factor of 2.5 reflects the relative bioavailability of calcidiol vs vitamin D_3 under the proposed conditions of use and use levels, and that it is safe under the proposed conditions of use and use levels, i.e. up to 10 μg/day for children ≥ 11 years old and adults, including pregnant and lactating women, and up to 5 μg/day for children 3–10 years of age.

KEYWORDS

25-hydroxycholecalciferol monohydrate, calcidiol monohydrate, conversion factor, food supplement, novel food, tolerable upper intake level, vitamin D

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1 | INTRODUCTION

1.1 | Background as provided by the European Commission

Following a request from the Commission, on 25 May 2021, EFSA adopted a scientific opinion on "Safety of calcidiol monohydrate produced by chemical synthesis as a novel food pursuant to Regulation (EU) 2015/2283,"[1] including its bioavailability as a metabolite of vitamin D_3 when added for nutritional purposes to food supplements.

In its opinion, EFSA concluded that calcidiol monohydrate is safe under the proposed conditions of use and use levels for individuals ≥ 11 years old, including pregnant and lactating women and that it is a bioavailable source of the biologically active metabolite of vitamin D, i.e. 1,25-dihydroxyvitamin D. It was further noted that *"a systematic review of data, assessing the extent to which oral calcidiol is more bioavailable than oral vitamin D_3 in all population groups and dietary context was outside the remit of this opinion and the data provided by the applicant do not permit this question to be answered for the proposed daily intake of 5 or 10 µg/day. Thus, as a theoretical calculation for this opinion, the NDA Panel used the factor of 5 set by the FEEDAP Panel to convert calcidiol to vitamin D."*

Annex II to Directive 2002/46/EC[2] lists the chemical substances that may be used as forms of vitamins and minerals in the manufacture of food supplements. Article 6(3) of the same Directive provides that the amount of nutrients or substances with a nutritional or physiological effect present in the product shall be declared on the labelling in numerical form. Concerns have been raised by the Member States that the absence of a conversion factor that would allow to convert the amount of calcidiol monohydrate into vitamin D_3 might cause difficulties for the national competent authorities in enforcing compliance with the abovementioned provision. In addition, both Regulation (EU) No 1169/2011[3] and Directive 2002/46/EC foresee that the information on vitamins and minerals in a product shall be expressed as a percentage of the daily reference intakes. Annex XIII of Regulation (EU) No 1169/2011 lists these daily reference intakes, including that for vitamin D, without providing for a conversion factor that would allow to convert the amount of calcidiol monohydrate into vitamin D. Therefore, on 25 February 2022, the Commission requested EFSA to assess the extent to which calcidiol monohydrate is bioavailable as compared to native vitamin D_3, as well as to derive a conversion factor that allows converting absolute amounts of this nutrient form into vitamin D_3.

On 5 July 2023, EFSA adopted "Scientific opinion on the tolerable upper intake level for vitamin D, including the derivation of a conversion factor for calcidiol monohydrate."[4] This opinion concerns an updated exposure assessment for vitamin D and proposes a conversion factor for calcidiol monohydrate into vitamin D_3 of 2.5 for labelling purposes.

In addition, in reference to the EFSA opinion on the safety of calcidiol monohydrate, the Commission has received a letter from the pharmaceutical company EirGen Pharma Ltd requesting a revision on this opinion on the basis of new data concerning calcidiol.

1.2 | Terms of reference as provided by the European Commission

In accordance with Article 31 of Regulation (EC) 178/2002, the European Commission asks the European Food Safety Authority to provide scientific and technical assistance as regards the evaluation of calcidiol monohydrate as a novel food.

In particular, EFSA is requested to re-consider the outcome of the opinion on the safety of calcidiol monohydrate under the conditions of use proposed by the applicant in light of:

a. the EFSA "Scientific opinion on the tolerable upper intake level for vitamin D, including the derivation of a conversion factor for calcidiol monohydrate" establishing the conversion factor for calcidiol monohydrate into vitamin D_3 of 2.5 and updating the exposure assessment for vitamin D, and
b. the new data provided by the company EirGen Pharma Ltd.

1.3 | Interpretation of the terms of reference

EFSA interprets the mandate from the European Commission as a request to consider whether the conclusions of the NDA Panel on the safety of calcidiol monohydrate under the conditions of use proposed by the applicant (EFSA NDA Panel, 2021) could change in view of the new information and data highlighted in the ToR. To that end, EFSA is requested to address whether:

[1]EFSA Journal 2021;19(7):6660.

[2]Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. OJ L 183, 12.7.2002, pp. 51–57.

[3]Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers. OJ L 304, 22.11.2011, p. 18.

[4]EFSA Journal 2023;21(8):8145.

a. calcidiol monohydrate (25-hydroxycholecalciferol monohydrate) is safe under the proposed conditions of use and use levels (up to 10 µg/day) for children ≥ 11 years old and adults, including pregnant and lactating women; and
b. conclusions on the safety of consumption of calcidiol monohydrate by children 3–10 years of age at the proposed daily intake of 5 µg/day can be reached with the information and data currently available.

2 | DATA AND METHODOLOGIES

2.1 | Data

The following information and data will be used in the present scientific technical report.

a. The EFSA scientific opinion on the safety of calcidiol monohydrate produced by chemical synthesis as a novel food (NF) pursuant to Regulation (EU) 2015/2283 (EFSA NDA Panel, 2021).
b. The EFSA scientific opinion on the tolerable upper intake level for vitamin D, including the derivation of a conversion factor for calcidiol monohydrate (EFSA NDA Panel, 2023).
c. The letter sent by EirGen Pharma Ltd to the European Commission dated 13 April 2023.
d. The recent publication 'Evaluation of therapies for secondary hyperparathyroidism associated with vitamin D insufficiency in chronic kidney disease' (Strugnell et al., 2023) mentioned by EirGen Pharma Ltd in the letter as new source of evidence to be considered in the safety assessment of calcidiol monohydrate as NF.

2.2 | Methodologies

Intake estimates of vitamin D from all sources, including the NF, will be re-calculated for all pertinent population groups in view of the newly available data using a similar methodology to that described in the safety assessment of calcidiol monohydrate (EFSA NDA Panel, 2021).

Uncertainties in the body of evidence will be discussed narratively.

3 | ASSESSMENT

3.1 | Proposed conditions of use and use levels of the NF that are relevant to this scientific technical report

The following information is extracted from the EFSA scientific opinion on the safety of calcidiol monohydrate (EFSA NDA Panel, 2021).

The applicant intends to market the NF as a diluted form called '0.25% w/w' or 'Calcidiol 0.25% SD/S'. This formulation contains values in the range of 0.250%–0.275% w/w of calcidiol (anhydrous), and thus 0.25% w/w is only the lower bound of the content range.

a. The proposed maximum daily intake is 10 µg of the NF per day for children aged 11 years and above, as well as for adults including pregnant and lactating women. For children of age 3–10 years, the proposed maximum daily intake of the NF is 5 µg/day.
b. The quantity of the commercial preparation '0.25% w/w' indicated by the applicant is 4 mg/day (anhydrous calcidiol, powder) to reach the proposed daily NF intake of 10 µg.

Therefore, presumably 2 mg of the commercial preparation '0.25% w/w' are indicated to reach the proposed daily intake of calcidiol monohydrate of 5 µg/day for children 3–10 years of age.

Given that concentrations up to 0.275% w/w of calcidiol could be present in the formulation, intakes of calcidiol monohydrate up to 11 µg/day and up to 5.5 µg/day could be achieved by adults and children, respectively, following the manufacturer instructions to consume 4 and 2 mg/day of the product, respectively.

It is important to note that, under the proposed conditions of use, calcidiol monohydrate as NF is consumed daily. This means that EFSA has evaluated the safety of calcidiol monohydrate only at daily doses up to 10 and 5 µg for adults and children, respectively, but not of supplementation patterns less frequent than daily (e.g. the safety of 70 µg/week, or 300 µg/month, corresponding to daily doses of 10 µg for adults).

In addition, the target population was the general healthy population 3 years of age and older, including pregnant and lactating women. The safety of calcidiol monohydrate for the treatment of medical conditions (e.g. secondary hyperparathyroidism associated with hypovitaminosis D in end-stage chronic kidney disease (CKD)) is not within EFSA's remit and therefore has not been assessed by EFSA.

3.2 | Derivation of a conversion factor for calcidiol monohydrate and associated uncertainties

Upon request from the European Commission, EFSA has derived a conversion factor (CF) for calcidiol monohydrate in the context of setting tolerable upper intake levels (ULs) for vitamin D from all sources (EFSA NDA Panel, 2023).

Both for setting the UL for vitamin D and for deriving a conversion factor for calcidiol monohydrate, randomised controlled trials (RCTs) on vitamin D supplementation pattern less frequent than weekly were excluded, owing to the uncertainties associated to the extrapolation of the results from these studies to the health effects of daily doses of vitamin D, which are the basis for deriving Dietary Reference Values (DRVs) for nutrients, including ULs. It was also considered that the safety of calcidiol in food supplements had been assessed for daily doses only.

The derivation of the CF was based on a systematic review of RCTs comparing the effect of weekly or daily doses of calcidiol vs vitamin D_3 given for at least 6 weeks on serum 25(OH)D, the selected marker of vitamin D status. A total of 10 RCTs were eligible for data analysis. The relative bioavailability of calcidiol vs native vitamin D_3 in equimolar amounts had been assessed only at doses of 20 and 25 µg/day. At 20 µg/day, the mean relative bioavailability of calcidiol ($n = 5$ RCTs) was 2.02 (95% CI: 1.85, 2.21) times that of vitamin D_3 and dropped to 1.31 (95% CI: 1.26, 1.37) times at 25 µg/day (only 1 RCT available). The mean relative bioavailability of calcidiol compared to vitamin D_3 obtained in the meta-analysis including all RCTs available and all calcidiol arms was 2.4 (95% CI: 1.89, 3.06), dropping to 2.11 (95% CI:1.82, 2.46) when the two RCTs that used ~60 µg/day vitamin D_3 as the reference dose were excluded in sensitivity analyses. Taking into account that the use of calcidiol in food supplements had been considered safe at intake levels up to 10 µg/day (EFSA NDA Panel, 2021), and that the relative bioavailability of calcidiol vs vitamin D_3 consistently increased with decreasing doses of calcidiol in the four RCTs that used multiple calcidiol doses, the NDA Panel considered that a CF of 2.5 reflected the relative bioavailability of calcidiol as proposed for use in food supplements.

The 10 RCTs used to derive the CF for calcidiol include healthy male and female adults and populations with low and adequate vitamin D status, mostly 50 years of age and older. Since intestinal absorption of vitamin D_3 does not appear to be significantly affected by age (Borel et al., 2015), the NDA Panel considered that the CF for calcidiol derived from those studies could apply to all population groups that are the target population for the use of calcidiol in food supplements and for which the safety of calcidiol monohydrate had been established in the safety evaluation as NF (11 years of age and older).

The main uncertainties associated with the proposed CF for calcidiol monohydrate relate to data gaps in the body of evidence, mostly in relation to the reference dose of vitamin D_3 used in the studies, and the bioequivalence of calcidiol vs vitamin D_3. Whereas the effect of calcidiol on serum 25(OH)D concentrations was assessed over a wide range of intakes in the available RCTs (5–38 µg/day), vitamin D_3 was used as reference only at doses of 20–25 µg/day or ~ 60 µg/day. At intakes of calcidiol of 20 µg/day, the dose of vitamin D_3 used as comparator (20 µg/day vs ~ 60 µg/day) had a big impact on the relative bioavailability per µg/day of vitamin D administered (~ 2 vs ~ 4.5). The NDA Panel noted the lack of eligible studies comparing equimolar doses of calcidiol vs vitamin D_3 at < 20 µg/day, which could provide a better estimate of the CF for calcidiol monohydrate over that range of intake.

Serum parathyroid hormone (PTH) concentrations were reported in seven of the above-mentioned RCTs. The consistent finding that calcidiol was more effective in increasing serum 25(OH)D concentrations than vitamin D_3 but not more effective in concomitantly suppressing serum PTH concentrations reflected the need to elucidate further the biological activity of the two forms of the vitamin.

The NDA Panel noted that the dose, frequency and duration of supplementation with both calcidiol monohydrate and vitamin D_3 were likely to have an impact on the achieved serum 25(OH)D concentrations, and thus on the relative bioavailability of calcidiol monohydrate vs the reference (vitamin D_3). Hence, the CF derived for calcidiol monohydrate applies in the context of the criteria used for study selection in the UL opinion for vitamin D regarding the frequency of supplementation (daily or weekly doses) and the minimum duration of the intervention (6 weeks).

From a scientific point of view, the NDA Panel considered that the biological value of substances with vitamin D activity could be expressed as vitamin D equivalents (VDE), so that 1 µg VDE = 1 µg cholecalciferol (vitamin D_3) =1 µg ergocalciferol (vitamin D_2) = 0.4 µg calcidiol monohydrate = 40 IU. This applies to calcidiol monohydrate at doses up to 10 µg/day.

The UL for adults including pregnant and lactating women, and for children aged 11–17 years, was set at 100 µg VDE/day (EFSA NDA Panel, 2023). The UL covers dietary intake of vitamin D from all sources, including fortified foods and food supplements. It applies to all forms of vitamin D authorised for addition to foods and food supplements (i.e. vitamins D_2 and D_3), and to calcidiol monohydrate. Regarding calcidiol monohydrate, the Panel noted that safety had been established up to 10 µg/day for these population groups (EFSA NDA Panel, 2021), which corresponds to 25 µg VDE/day considering a CF for calcidiol monohydrate into vitamin D_3 of 2.5. The UL for children 1–10 years was set at 50 µg VDE/day by considering their smaller body size.

3.3 | Intake estimates for vitamin D from all sources including the NF under the proposed conditions of use and use levels

In the safety assessment of calcidiol monohydrate as NF (EFSA NDA Panel, 2021), vitamin D intakes up to 49.4, 70.2 and 78.8 µg/day for children 3–10 years, adolescents and adults, respectively, were calculated using a conversion factor of 5 for calcidiol monohydrate into vitamin D (EFSA FEEDAP Panel, 2009) and the highest (P95) vitamin D (D_2, ergocalciferol, and D_3,

cholecalciferol) intakes from the background diet reported in national food consumption surveys (EFSA NDA Panel, 2012). The contribution of fortified foods was not included in the calculation.

Table 1 shows a recalculation of vitamin D intake estimates from calcidiol (including background intake and the NF at the maximum proposed used levels) and vitamin D (D_2 and D_3) from both the background diet and fortified foods. Food supplements other than calcidiol are excluded. To that end, the following data from the newly available EFSA scientific opinion on the UL for vitamin D (EFSA NDA Panel, 2023) have been used:

a. a factor of 2.5 for the conversion of the intake of calcidiol monohydrate into VDE;
b. the most recent, harmonised vitamin D intake data from the background diet that is currently available. Intake estimates across population groups and European countries were calculated using the EFSA Comprehensive food consumption and the EFSA food composition databases;
c. combined intakes of vitamin D from the background diet and fortified foods based on published data from national food consumption surveys.

Sources of uncertainty in the intake estimates for vitamin D from the background diet and fortified foods are discussed in the scientific opinion (EFSA NDA Panel, 2023).

TABLE 1 Intake estimates for vitamin D from the background diet, fortified foods and calcidiol from the background diet and supplements at the highest use levels proposed by the applicant.

Intake estimates	Population group		
	Children (≥ 3 to 10 years)	Adolescents (≥ 11 to < 18 years)	Adults (≥ 18 years)
Total intake of calcidiol (μg/day)[a]	7.5	12.5	12.5
Total intake of calcidiol expressed as vitamin D (μg VDE/day)[b]	18.8	31.3	31.3
Highest P95 intake of vitamin D from the background diet (μg/day)[c]	8.0	11.9	16.1
Highest intake of vitamin D from the background diet + fortified foods (μg/day)[d]	11.7	13.1	19.5
Combined intake of vitamin D (background diet) and calcidiol (μg VDE/day)[e]	26.8	43.2	47.4
Combined intake of vitamin D (background diet + fortified foods) and calcidiol (μg VDE/day)[f]	30.5	44.4	50.8
UL for vitamin D (μg VDE/day)[g]	**50**	**100**	**100**

Abbreviation: VDE, vitamin D equivalents.

[a]Resulting from the combined intake of calcidiol (25-hydroxycholecalciferol) from the NF under the proposed conditions of use (5 or 10 μg/day) and from the background diet (2.44 μg/day) according to the refined calculation of the EFSA FEEDAP Panel (2009).

[b]Vitamin D intake resulting from the combined intake of calcidiol from the NF and the background diet using a conversion factor of 2.5.

[c]Background intake of vitamin D_2 and vitamin D_3 from foods, excluding fortified foods. Figures correspond to the highest P95 for the relative age category.

[d]Combined intakes of vitamin D_2 and vitamin D_3 from the background diet and fortified foods based on published data from national food consumption surveys. Figures correspond to the highest reported P95 for the relative age category. The highest P95 reported for toddlers is used for children 3–10 years, as intake estimates for this specific age category were not available.

[e]Resulting from the sum of the combined intake of calcidiol from the NF and the background diet (μg VDE/day), and the highest intake of vitamin D from the background diet.

[f]Resulting from the sum of the combined intake of calcidiol from the NF and the background diet (μg VDE/day), and the highest intake of vitamin D from the background diet and fortified foods.

[g]From EFSA NDA Panel (2023).

3.4 | Safety of calcidiol monohydrate under the proposed conditions of use and use levels (up to 10 μg/day) for adolescents (≥ 11 years old) and adults, including pregnant and lactating women

In the safety assessment of calcidiol monohydrate as NF (EFSA NDA Panel, 2021), the NDA Panel concluded that calcidiol monohydrate was safe for children ≥ 11 years old (adolescents) and adults, including pregnant and lactating women, under the proposed conditions of use and use levels (food supplements to be consumed daily at doses up to 10 μg/day).

A total of six RCTs in adults reported in eight publications comparing calcidiol vs vitamin D_3 were submitted by the applicant (Barger-Lux et al., 1998; Bischoff-Ferrari et al., 2012; Cashman et al., 2012; Jetter et al., 2014; Kunz et al., 2016; Navarro-Valverde et al., 2016; Vaes et al., 2018; Wittwer, 2015).[5]

The conclusion of the NDA Panel was based on the following reasons:

[5]Bischoff-Ferrari et al. (2012) and Jetter et al. (2014) are two publications on the same study. Wittwer (2015) is the unpublished study report and the corresponding publication is Vaes et al. (2018).

a. calcidiol monohydrate did not raise serum 25(OH)D concentrations above 107 nmol/L and did not increase the risk of hypercalcaemia, hypercalciuria or other adverse health effects at doses up to 10 µg/day in RCTs. The duration of the intervention ranged from 4 weeks to 12 months, depending on the study; and
b. conservative, total combined vitamin D intake estimates from calcidiol (NF + background diet) and vitamin D (highest P95) from the background diet (up to 70.2 and 78.5 µg/day for adolescents and adults, respectively) were well below the UL for adolescents and adults, including pregnant and lactating women (100 µg/day).

The NDA Panel considered that, although bioavailability (i.e. the impact on serum 25(OH)D concentrations) and safety data were lacking for pregnant and lactating women, the data available for adults were sufficient to cover these population groups. Using newly available data (EFSA NDA Panel, 2023), including fortified foods in the estimate, and using a CF of 2.5, highest intake estimates for vitamin D excluding food supplements other than the NF (up to 44.4 and 50.8 µg VDE/day for adolescents and adults, respectively; Table 1) remain well below the UL for adolescents and adults, including pregnant and lactating women (100 µg VDE/day).

On its letter of 23 April 2023 to the European Commission, EirGen Pharma Ltd raised concerns about the authorisation of calcidiol monohydrate as a NF. The main points raised in the letter are the following:

1. *'The Panel apparently made the assumption that vitamin D (either cholecalciferol or ergocalciferol) and calcidiol are both safe because they work by the same mechanism (supporting adequate renal production of vitamin D hormones) and do not raise serum 25D to an excessive level at the approved dosages. Following that same logic, vitamin D, calcidiol and calcitriol should all be considered safe for treating secondary hyperparathyroidism (SHPT) because they work by the same mechanism (supporting adequate supply of vitamin D hormones to the parathyroid glands) at appropriate doses that do not over-suppress parathyroid hormone (PTH) levels, a surrogate endpoint for adynamic bone disease'*.

The NDA Panel did assume that hypercalcaemia and hypercalciuria are adverse health effects to be expected from excess intake of both vitamin D (either cholecalciferol or ergocalciferol) or calcidiol, and that in both cases the effect would be mediated by an increase in serum 25(OH)D concentrations (EFSA NDA Panel, 2021). Owing that the critical effect to derive a UL for vitamin D was persistent hypercalcaemia/hypercalciuria, the Panel considered that the UL applies to all forms of vitamin D authorised for addition to foods and food supplements (i.e. vitamins D_2 and D_3), and to calcidiol monohydrate up to 10 µg/day (EFSA NDA Panel, 2021).

Calcitriol (1,25 $(OH)_2D$), the active form of vitamin D, does not raise serum 25(OH)D concentrations and does not need activation by the kidney. Therefore, the mechanisms of toxicity for calcitriol are different from those of cholecalciferol, ergocalciferol or calcidiol.

2. *'Vitamin D (either ergocalciferol or cholecalciferol) is a dietary supplement with extensive safety data in the general population; in contrast, calcidiol and calcitriol are prescription drugs for which adequate safety data have been generated only in narrowly defined populations. The data on which the Panel relied in deeming calcidiol to be safe are woefully inadequate. […] These studies, listed in Appendix A of the report, involved only a small number of adults dosed with 10 or more µg/day of calcidiol but no children or pregnant/lactating women. The number treated and the duration of dosing are insufficient for adequate exposure to establish the safety of calcidiol as a medicinal product not subject to a prescription, given that two of the studies did not report urine calcium, one did not define hypercalcemia and four did not monitor or report adverse events'*.

Contrary to calcitriol, calcidiol is naturally present in foods of animal origin. Intakes up to 2.44 µg/day have been estimated by EFSA (EFSA FEEDAP Panel, 2009). In the last EFSA scientific opinion on the UL for vitamin D (EFSA NDA Panel, 2023), a systematic review was conducted to retrieve RCTs investigating the relationship between vitamin D supplementation and persistent hypercalcaemia/hypercalciuria, as defined by the authors, with an intervention period of at least 6 weeks (i.e. the time estimated to reach plateau serum 25(OH)D concentrations after the start of the intervention). The definition of persistent hypercalcaemia/hypercalciuria was often unclear in the studies identified; therefore, the systematic approach was implemented and as such, a case of persistent hypercalcaemia/hypercalciuria was defined as a participant with elevated calcium concentrations in blood/urine (as defined within each study) that were confirmed through repeated testing, or who experienced recurrent elevated levels during the study period. Transient cases (i.e. which resolved on re-testing or subsequent follow-up visits) were not included in the analysis, while cases that were unclear as to whether they were transient or persistent were included in the evidence synthesis but specifically noted as uncertain and excluded in sensitivity analyses, if applicable.

In the context of the systematic review, data were not extracted for 31 RCTs investigating vitamin D doses < 100 µg/day in adults and < 50 µg/day in children (i.e. below the current UL for vitamin D for the respective population groups) (see appendix E in EFSA NDA Panel, 2023). This was because, below these values, cases of hypercalcaemia or hypercalciuria did not occur, were not persistent, and/or could not be related to the vitamin D dose administered (i.e. the treatment group in which it occurred was not specified in the publication, the number of cases was higher at lower doses of vitamin D, and/or persistent cases occurred in patients with primary hyperparathyroidism). Among these, 5 RCTs (Cashman et al., 2012; Gonnelli et al., 2021; Graeff-Armas et al., 2020; Minisola et al., 2017; Vaes et al., 2018) investigated calcidiol at doses from 5 to 40 µg/day given for 10 weeks to 6 months. All the studies were in adults.

Together with the RCTs assessed by the NDA Panel in the safety assessment of calcidiol as NF (EFSA NDA Panel, 2021), the available evidence indicates that doses of calcidiol up to 10 µg/day do not raise safety concerns for the general healthy adult population and this conclusion can be extended to adolescents (≥ 11 to 18 years of age), as there is no reason to believe that adolescents in the phase of rapid bone formation and growth have a lower tolerance for vitamin D compared to adults.

Bioavailability and safety data for calcidiol monohydrate are indeed lacking for children 3–10 years of age (see Section 3.5) and for pregnant and lactating women. However, the NDA Panel considered that the data available for adults were sufficient to cover pregnant and lactating women because, up to 10 µg/day of calcidiol, no increased risk of hypercalcaemia or hypercalciuria was expected from the observed increase in serum 25(OH)D concentrations at these levels of intake, and the highest vitamin D intake estimates were well below the UL for these population groups.

3. *'Calcidiol, cholecalciferol and ergocalciferol all belong to the established vitamin D class, but are not identical chemical entities. They have markedly different physical and biological characteristics and, as mentioned previously in our letter of 16 February 2022, have great pharmacokinetic differences, a fact the Panel appears to have ignored. Cholecalciferol and ergocalciferol produce peak serum total 25D levels several days after dosing,[6] are fat soluble molecules which travel in the mesenteric lymph after intestinal absorption in chylomicrons,[7] and accumulate preferentially in adipose tissue.[8] They have low affinities for the serum-based vitamin D binding protein (DBP),[9] are poorly drawn out of adipose into circulation for hepatic activation,[10] and are prone to in situ catabolism by CYP24A1, the vitamin D catabolic enzyme that can be upregulated in CKD and other diseases which are highly prevalent in the general population.[11] Hepatic 25-hydroxylase activity is reduced in both obesity[12] and CKD,[13] slowing the intended elevation of serum total 25D.[14] In contrast, immediate-release calcidiol (IRC) rapidly produces peak serum 25D levels (at approximately 6 h),[15] requires no hepatic activation, is more water soluble, and travels in mesenteric lymph bound to DBP (not in chylomicrons).[7] It is stored, contrary to the Panel's conclusion, in serum bound to DBP, which reduces its accumulation in adipose tissue, muscle and liver and enables its circulation to the kidney and to other tissues containing the 1a-hydroxylase (CYP27B1) for both endocrine and intracrine conversion to calcitriol, respectively.[16] Gradual delivery of calcidiol from ERC[17] produces peak serum total 25D levels after 30 or more hours (even after many days), has been shown to cause minimal suppression of CYP27B1 and minimal upregulation of CYP24A1 whereas IRC, proposed by the Panel as an NF, effectively suppresses CYP27B1 and markedly upregulates CYP24A1, making vitamin D-responsive tissues less capable of producing calcitriol and more likely to become locally vitamin D deficient.[18] The long-term safety consequences of disrupting the delicate balance between CYP27B1 and CYP24A1 in these tissues is poorly understood and clearly unaddressed by the six human intervention studies cited by the Panel'.*

In its scientific opinion on the UL for vitamin D (EFSA NDA Panel, 2023), the NDA Panel reviewed differences in the pharmacokinetics of calcidiol vs vitamin D_3. Indeed, absorption of vitamins D_2 and D_3 occurs mostly in the distal small intestine and is dependent on the presence of bile acids and micelle formation. Vitamins D_2 and D_3 are then incorporated into chylomicrons, which reach the systemic circulation through the lymphatic system. Conversely, intestinal absorption of the hydroxylated form of vitamin D_3 calcidiol does not require the presence of bile acids and micelle formation, and thus is faster and more efficient (about 93%, even in individuals with fat malabsorption) than that of the non-hydroxylated vitamins D_2 and D_3. After intestinal absorption, calcidiol reaches the systemic circulation via the portal vein.

Vitamin D_3 from dermal synthesis is transported in plasma bound to the specific vitamin D–binding protein (DBP), whereas dietary vitamins D_2 and D_3 (from food and supplements) are transported in chylomicrons, with some transfer to DBP. 25(OH)D resulting from hydroxylation of vitamins D_2 and D_3 primarily in the liver and from the intestinal absorption of calcidiol is transported in blood bound to DBP (85%–90%), albumin (10%–15%) or free (< 1%). The scientific opinion also clarifies that about 75% of vitamin D_3 is stored in adipose tissue, whereas 25(OH)D is more evenly distributed

[6]Armas LAG, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab* 2004;89:5387–5391.

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through the body (approximately 35% in adipose tissue, 30% in blood, 20% in muscle and 15% in other tissues) and that, compared to vitamin D_3, calcidiol monohydrate gives rise to a rapid and sustained increase in serum 25(OH)D concentrations due to differences in the absorption pathway and the hydroxylation of native vitamin D_3 in the liver, which delays the increase in the serum 25(OH)D concentration of the vitamin as compared to calcidiol monohydrate (EFSA NDA Panel, 2023).

The reference provided by EirGen Pharma Ltd to make the point that immediate release calcidiol effectively suppresses CYP27B1 and markedly upregulates CYP24A1 is, however, misleading in the context of this assessment (Petkovich et al., 2015). It refers to a study in which vitamin D deficient rats and then patients with end-stage (3 or 4) CKD and associated secondary hyperparathyroidism (SHPT) received single doses of either bolus intravenous (i.v.) calcidiol (450 µg for patients) or oral modified-release (MR) calcidiol (450 or 900 µg for patients). The paper discusses that bolus i.v. calcidiol produced rapid increases in serum 25(OH)D, calcitriol and fibroblast growth factor 23 (FGF23), along with a significant induction of CYP24A1 in both the kidney and parathyroid gland, and that a 10-fold greater exposure to bolus i.v. than to oral MR calcifediol was required to similarly lower intact parathyroid hormone (iPTH) in rats. In humans, i.v. calcidiol induced abrupt and pronounced increases in serum 25(OH)D_3 and calcitriol, but little change in plasma iPTH. The authors discuss the implications of these findings on the clinical efficacy (but not the safety) of different medicinal formulations of calcidiol (immediate vs modified release) to treat SHPT in patients with CKD.

As previously discussed, dose, frequency and duration of supplementation with vitamin D or calcidiol are likely to have an impact on the achieved serum 25(OH)D concentrations and the potential adverse health effects deriving from excess intake (EFSA NDA Panel, 2023). The route of administration is also likely to have a role. In the study mentioned (Petkovich et al., 2015), immediate-release calcidiol was administered i.v. at very high bolus doses to patients with end-stage CKD and SHPT. In the safety assessment of calcidiol as NF and in the derivation of a UL for vitamin D (including calcidiol at doses up to 10 µg/day), only studies providing daily (or weekly) oral doses to healthy adults were considered as pertinent for the safety evaluations.

When deriving a CF for calcidiol monohydrate vs vitamin D_3, the NDA Panel noted that, using data from the 7 (out of 10) RCTs also reporting on serum PTH concentrations, calcidiol raised serum 25(OH)D about twice as much than vitamin D_3 when given at similar doses of 20 µg/day and that this relative effect on serum 25(OH)D increased with decreasing doses of calcidiol in a dose–response manner. However, this was not reflected in a similar efficacy in reducing serum PTH concentrations, as similar doses of calcidiol and vitamin D_3 were required to equally suppress PTH. The NDA Panel also noted that the consistent finding that calcidiol was more effective in increasing serum 25(OH)D concentrations than vitamin D_3 but not in concomitantly suppressing serum PTH concentrations reflected the need to elucidate further the biological activity of the two forms of the vitamin. Here again the uncertainty raised by the NDA Panel refers to the 'clinical efficacy' of calcidiol, not to its safety.

4. *'EirGen has recently compared orally administered IRC and ERC in two randomized clinical trials involving patients with SHPT, stage 3–4 CKD and vitamin D insufficiency.*[19] *The more recent trial confirmed the conclusions of the earlier one, namely that the pharmacokinetics and pharmacodynamics of these treatments differ greatly. The data obtained are pertinent to individuals without kidney disease because it is known that CKD does not affect the intestinal absorption of vitamin D or its metabolites.*[20] *Sixteen subjects were assigned to cholecalciferol (7500 µg per month, equivalent to 250 µg/day) and evaluated, 15 to IRC (266 µg per month, equivalent of 8.9 µg/day), 17 to ERC (60 µg/day) and 14 to vitamin D hormone (1–2 µg paricalcitol/day). The bioavailabilities of cholecalciferol, IRC and ERC were approximately 75%, 80% and 25%, respectively, yielding bioavailable doses of 187.5, 7.1 and 15.0 pg/day. The selected dose of IRC (Hidroferol) is routinely used in Europe, and the ERC dose is used in both Europe and the US. All three study interventions raised serum 25D to varying degrees, but IRC produced peak serum calcidiol levels at approximately 6 h vs cholecalciferol at 18 h and ERC at 30 or more hours post dose. IRC produced PTH reductions from pre-treatment baseline that were consistently lower than those observed with either cholecalciferol or ERC and sudden increases in serum 24,25-dihydroxyvitamin D_3 (the primary catabolite of calcidiol) of 17.8% and 20.5% in the two 24-h periods following dosing on Days 1 and 29; in contrast, the corresponding increases in serum 24,25-dihydroxyvitamin D_3 observed with cholecalciferol were 5.6% and 6.8%, and with ERC were 0.0% and 2.6%, respectively. These data show that differences in pharmacokinetics matter: IRC increased the intracellular catabolism of vitamin D metabolites to a much greater extent than either cholecalciferol or ERC, despite a substantially lower bioavailable dose. Further, they indicate that IRC effectively reduced the delivery of calcitriol to the vitamin D receptors in target tissues, the long-term safety consequences of which are unknown but require proper evaluation'.*

The new study submitted by EirGen Pharma Ltd (Strugnell et al., 2023) is another RCT on the clinical efficacy of different vitamin D formulations in patients with end-stage (grade 3 or 4) CKD, vitamin D insufficiency (serum 25(OH)D < 30 ng/mL) and associated SHPT. Whereas ERC (60 µg/day) and paricalcitol plus low-dose cholecalciferol (PLDC; 1 or 2 µg/day paricalcitol plus 20 µg/day cholecalciferol) were given daily, immediate release calcidiol (IRC; 266 µg/month) and vitamin D_3 (7500 µg/

[19]Strugnell SA, Csomor P, Ashfaq A, et al. Evaluation of therapies for secondary hyperparathyroidism associated with vitamin D insufficiency in chronic kidney disease. *Kidney Dis* 2023. https://doi.org/10.1159/000529523.

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month) were given monthly for 2 months. The authors discuss that ERC was more effective in increasing serum 25(OH)D and suppressing iPTH than other treatments, and that IRC did not effectively increase 25(OH)D or suppress iPTH. Besides the fact that neither the dose of vitamin D nor the pattern of consumption of these formulations are comparable, the discussion above is about clinical efficacy and not safety.

EirGen Pharma Ltd also argues that the data obtained are pertinent to individuals without kidney disease because it is known that CKD does not affect the intestinal absorption of vitamin D or its metabolites (Strugnell et al., 2023). It is well known that CKD leads to changes in vitamin D metabolism, calcium and phosphate homeostasis, and bone metabolism, leading to CKD metabolic bone disease (CKD–MBD). The reasons for this are multifactorial. Supply of vitamin D may be lower because of lower cutaneous vitamin D production due to skin hyperpigmentation, ageing, sun avoidance and dietary restrictions, all reasons that may also apply to the general population of older adults. However, in advanced CKD, vitamin D losses increase through proteinuria, and hepatic conversion of vitamin D into 25(OH)D is reported to be suppressed. Even more relevant to this case is that, with the loss of functional renal tissue, the capacity to convert 25(OH)D to $1,25(OH)_2D$ (calcitriol) is increasingly reduced with the worsening of renal function, leading to a decline in plasma $1,25(OH)_2D$, the active form of vitamin D. The combination of these mechanisms leads to SHPT in CKD, and to CKD-MBD (Christodoulou et al., 2021).

In summary, the references provided by EirGen Pharma Ltd refer to interventions in patients that are not the target population for calcidiol monohydrate as a NF, and which provide calcidiol with a frequency of administration and/or at doses and/or through a route of administration that are not relevant to the proposed uses and use levels for calcidiol, monohydrate as a NF. In addition, the concerns raised by EirGen Pharma Ltd primarily refer to the clinical efficacy of calcidiol in correcting vitamin D insufficiency and SHPT in patients with CKD, rather than to the safety of calcidiol for the general healthy population. Therefore, the new data available (Section 2.1) do not put into question the safety of calcidiol monohydrate to be consumed daily by adolescents and adults, including pregnant and lactating women, at doses up to 10 µg/day.

3.5 | Safety of calcidiol monohydrate under the proposed conditions of use and use levels (up to 5 µg/day) for children 3–10 years old

In the safety assessment of calcidiol monohydrate as NF (EFSA NDA Panel, 2021), combined intake estimates of vitamin D for this population group (children 3–10 years) were calculated by using a factor of 5 for the conversion of calcidiol monohydrate into vitamin D_3 and intake estimates of vitamin D (D_2 and D_3) from the background diet, without considering the intake from fortified foods. In this context, the combined intake of the NF (5 µg/day) and calcidiol from the background diet, added to the background intake of vitamin D (D_2 and D_3), was 49.4 µg/day.

The NDA Panel could not conclude on the safety of calcidiol for the age group 3–10 years for the following reasons:

a. for high consumers, the combined intake of the NF (5 µg/day) and calcidiol from the background diet, added to the background intake of vitamin D (D_2 and D_3), would approach the UL for vitamin D of 50 µg/day for this population group;
b. the UL for vitamin D could be exceeded by the consumption of powder preparations containing calcidiol in the upper range (i.e. 0.275% w/w calcidiol) following the manufacturer instructions;
c. uncertainties in the intake estimates arising from the consumption of fortified foods newly available in the market could not be quantified;
d. no data were provided by the applicant to assess the bioavailability and safety of the consumption of the NF by children;
e. depending on the latitude and the time of the year, endogenous cutaneous vitamin D synthesis, impacting on serum 25(OH)D concentrations, was an additional uncertainty.

EFSA notes that, using a factor of 2.5 for the conversion of calcidiol monohydrate into vitamin D_3 and most updated available data on intake estimates of vitamin D from the background diet and fortified foods, the combined intake estimates of vitamin D for high consumers (P95) in the age range of 3–10 years would reach 30.5 µg VDE/day (Section 3.3). This value falls well below the UL for vitamin D (50 µg VDE/day) for this population group (EFSA NDA Panel, 2023). The UL takes into account vitamin D intake from all sources, including foods, fortified foods and food supplements, as well as endogenous cutaneous vitamin D synthesis.

In this context, EFSA also notes that the difference of 19.5 µg VDE/day between the combined vitamin D intake estimates in high consumers from all sources (i.e. including the NF up to 5 µg/day but excluding other food supplements) and the UL is sufficient to conclude on the safety of calcidiol monohydrate as NF for the age group 3–10 years for the following reasons:

a. the consumption of powder preparations containing calcidiol in the upper range (i.e. 0.275% w/w calcidiol) following the manufacturer instructions would lead to a maximum additional intake of 0.5 µg/day (Section 3.1), corresponding to 1.25 µg VDE/day;

b. intake estimates arising from the consumption of fortified foods have now been considered in the intake estimates for high consumers (Section 3.3);
c. in a meta-regression analysis of the serum 25(OH)D response to total vitamin D intake in adults and children based on data collected through 35 trials (83 arms) undertaken previously by EFSA (EFSA NDA Panel, 2016), age was not among the main factors affecting the dose–response relationship between the intake of vitamin D and serum 25(OH)D concentrations (EFSA NDA Panel, 2023);
d. although bioavailability and safety data for calcidiol monohydrate are lacking for children aged 3–10 years, the data available for adults is sufficient to cover this age group (up to 5 μg/day of calcidiol). No increased risk of hypercalcaemia or hypercalciuria was expected from the observed increase in serum 25(OH)D concentrations at intakes up to 10 μg/day of calcidiol in adults (Section 3.4; EFSA NDA Panel, 2021), and the highest combined vitamin D intake estimates for children aged 3–10 years are well below the UL for this population group (Section 3.3).

4 | CONCLUSION

Based on the information and data considered in this report (Section 2.1), EFSA concludes that the NF calcidiol monohydrate (25-hydroxycholecalciferol monohydrate) proposed for use in food supplements is:

a. a bioavailable source of the biologically active metabolite of vitamin D, i.e. 1,25-dihydroxyvitamin D. A conversion factor of 2.5 reflects the relative bioavailability of calcidiol vs vitamin D_3 under the proposed conditions of use and use levels;
b. safe under the proposed conditions of use and use levels (up to 10 μg/day) for children ≥ 11 years old and adults, including pregnant and lactating women; and
c. safe under the proposed conditions of use and use levels (up to 5 μg/day) for children 3–10 years of age.

DOCUMENTATION PROVIDED TO EFSA

1. Letter from the pharmaceutical company EirGen Pharma Ltd to the European Commission requesting a revision on the NF opinion (EFSA NDA Panel, 2021) based on new data concerning calcidiol.
2. Scientific publication submitted by EirGen Pharma Ltd to the European Commission (Strugnell et al., 2023).

ABBREVIATIONS

1,25(OH)2D	1,25-dihydroxyvitamin D, calcitriol
25(OH)D	25-hydroxyvitamin D
CF	conversion factor
CI	confidence interval
CKD	chronic kidney disease
DBP	vitamin D–binding protein
DRV	Dietary Reference Values
ERC	extended-release calcifediol
FEEDAP	Panel on Additives and Products or Substances used in Animal Feed
iPTH	intact parathyroid hormone
IRC	immediate-release calcifediol
MBD	mineral and bone disorder
MR	modified-release
NDA	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NF	Novel food
PLDC	plus low-dose cholecalciferol
PTH	parathyroid hormone
RCT	randomised controlled trial
SHPT	secondary hyperparathyroidism
UL	tolerable upper intake level
VDE	vitamin D equivalents
w/w	weight for weight

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CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

REQUESTOR

European Commission

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