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# COMMISSION IMPLEMENTING REGULATION (EU) 2024/1052

## of 10 April 2024

## authorising the placing on the market of calcidiol monohydrate as a novel food and amending Implementing Regulation (EU) 2017/2470

**(Text with EEA relevance)**

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001 ([1]), and in particular Article 12(1) thereof,

Whereas:

(1) Regulation (EU) 2015/2283 provides that only novel foods authorised and included in the Union list of novel foods may be placed on the market within the Union.

(2) Pursuant to Article 8 of Regulation (EU) 2015/2283, Commission Implementing Regulation (EU) 2017/2470 ([2]) has established a Union list of novel foods.

(3) On 16 May 2018, the company DSM Nutritional Products Ltd. ('the applicant') submitted an application to the Commission pursuant to Article 10(1) of Regulation (EU) 2015/2283 to place calcidiol monohydrate on the Union market as a novel food. The applicant requested for calcidiol monohydrate to be used as a novel food in food supplements as defined in Directive 2002/46/EC of the European Parliament and of the Council ([3]), intended for the general population above 3 years of age. The novel food was proposed for use in food supplements at levels of up to 10 µg/day for persons above 11 years of age and at levels of up to 5 µg/day for children from 3 to 10 years of age. The applicant also requested for calcidiol monohydrate to be added to the list of vitamin D forms specified in Annex II to Directive 2002/46/EC as a form of vitamin D.

(4) On 16 May 2018, the applicant also made a request to the Commission for the protection of proprietary data for a number of studies submitted in support of the application, namely, master data for calcidiol ([4]); a comparison of 25(OH)D concentration in human serum/plasma following oral supplementation of calcifediol or cholecalciferol ([5]); the comparative metabolism of [14C]-calcifediol and [14C]-cholecalciferol following multiple oral administration in the intact male han wistar rat ([6]); the comparative metabolism of [14c]-calcifediol and [14c]-cholecalciferol following single oral administration in the bile duct cannulated male han wistar rat ([7]); calcifediol: acute oral toxicity study in rats ([8]); an *in-vitro* skin irritation test with DSMO47J 17 using a human skin model ([9]); an evaluation of the eye hazard potential of DSMO47J 17 using the bovine corneal opacity and permeability test ([10]); an evaluation of the mutagenic activity of D5M0471 17 in an *in vitro* mammalian cell gene mutation test with L5178Y mouse lymphoma cells ([11]); assessment of skin sensitization to DSMO471J7 in the mouse (Local Lymph Node Assay) – pre-screen test ([12]); a micronucleus test in bone marrow cells of the rat with DSM047117 ([13]); a *Salmonella typhimurium* and *Escherichia coli* reverse mutation assay ([14]); a chromosome aberration test in human lymphocytes *in vitro* with calcifediol ([15]); a 90-day oral toxicity study with DSM0471 17 by dietary administration in the rat followed by

([1]) OJ L 327, 11.12.2015, p. 1, ELI: http://data.europa.eu/eli/reg/2015/2283/oj.
([2]) Commission Implementing Regulation (EU) 2017/2470 of 20 December 2017 establishing the Union list of novel foods in accordance with Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods (OJ L 351, 30.12.2017, p. 72, ELI: http://data.europa.eu/eli/reg_impl/2017/2470/oj).
([3]) 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, p. 51, ELI: http://data.europa.eu/eli/dir/2002/46/oj).
([4]) ANNEX 1_Friederich_Beck, master data calcifediol_PROPRIETARY UNPUBLISHED DATA.pdf
([5]) ANNEX 2_Beck 2016_RD 00053392_ PROPRIETARY UNPUBLISHED DATA.pdf
([6]) ANNEX 3_Beck et al 2017a_ PROPRIETARY UNPUBLISHED DATA.pdf
([7]) ANNEX 4_Beck et al 2017b_ PROPRIETARY UNPUBLISHED DATA.pdf
([8]) ANNEX 5_Weber & Arcelin_2004b_ PROPRIETARY UNPUBLISHED DATA.pdf
([9]) ANNEX 6_Remus_2016a_skin irritation_ PROPRIETARY UNPUBLISHED DATA.pdf
([10]) ANNEX 7_Remus_2016b_BCOP_ PROPRIETARY UNPUBLISHED DATA.pdf
([11]) ANNEX 8_Remus 2016c_MLA_ PROPRIETARY UNPUBLISHED DATA.pdf
([12]) ANNEX 9_Remus_2016d_LLNA_PROPRIETARY UNPUBLISHED DATA.pdf
([13]) ANNEX 10_Remus 2016e_in vivo MNT_PROPRIETARY UNPUBLISHED DATA.pdf
([14]) ANNEX 11_Woehrle & Sokolowski 2013_PROPRIETARY UNPUBLISHED DATA.pdf
([15]) ANNEX 12_Weber & Schulz 2005_PROPRIETARY UNPUBLISHED DATA.pdf

a 28-day recovery period ([16]); a 3-month oral toxicity study with Rovimix® D3-500 by dietary administration followed by a 4-week recovery period in Wistar rats ([17]); a dose finding study in physically non-frail and (pre-)frail elderly to measure 25(OH) vitamin D levels after supplementation with HY.D calcifediol 25 SD/S and vitamin $D_3$ ([18]); response of serum 25-hydroxyvitamin D to different doses of Calcifediol 0,25 SD/S compared to vitamin $D_3$ supplementation: a randomized, controlled, double blind, long term pharmacokinetic study ([19]); a report on the particle size distribution and its annexes ([20]).

(5) On 14 December 2018, the Commission requested the European Food Safety Authority ('the Authority') to carry out an assessment of calcidiol monohydrate as a novel food. The Commission also requested the Authority to evaluate, following the outcome of the novel food assessment, the safety and bioavailability of the novel food when added for nutritional purposes as a source of vitamin D to food supplements.

(6) On 25 May 2021, the Authority adopted its scientific opinion on the 'Safety of calcidiol monohydrate produced by chemical synthesis as a novel food pursuant to Regulation (EU) 2015/2283' ([21]) in accordance with Article 11 of Regulation (EU) 2015/2283.

(7) In its scientific opinion, the Authority concluded that calcidiol monohydrate is safe under the proposed conditions of use at use levels of up to 10 µg/day for the general population, excluding infants and children under 11 years of age. For children from 3 to 10 years of age the Authority concluded that combined intake of the novel food (5 µg/day) and of calcidiol from the background diet, added to the background intake of vitamin D, would approach the Tolerable Upper Intake Level (UL) for vitamin D ($D_2$ and $D_3$). Furthermore, as the novel food is proposed for use as a preparation containing 0,25 % to 0,275 % w/w of calcidiol, the UL for children of this age could be exceeded. Given the uncertainties, the Authority could not conclude on the safety of consumption of the novel food for children from 3 to 10 years of age at the proposed daily intake.

(8) The Authority also concluded that the novel food is a bioavailable source of the biologically active form of vitamin D (1,25-dihydroxyvitamin D). For the safety assessment, the Authority took a conservative approach for the theoretical calculation and used a factor of 5 set by the Panel on Additives and Products or Substances used in Animal Feed to convert calcidiol to vitamin D. However, the Authority also noted that a systematic review of data, to assess the extent to which oral calcidiol is more bioavailable than oral vitamin $D_3$ in all population groups and the dietary context was outside the remit of that opinion and the data provided by the applicant did not permit that question to be answered for the proposed daily intake of 5 or 10 µg/day.

([16]) ANNEX 13_Thiel et al 2014c_PROPRIETARY UNPUBLISHED DATA.pdf
([17]) ANNEX 14_Thiel et al 2007_PROPRIETARY UNPUBLISHED DATA.pdf
([18]) ANNEX 15_Wittwer 2015_D-Dose_study_PROPRIETARY UNPUBLISHED DATA.pdf
([19]) ANNEX 16_Kunz et al_2016_PROPRIETARY UNPUBLISHED DATA.pdf
([20]) Report DSM_EFSA_Calcifediol_CONF_DATA PROT_NEW_2_0121 (initial report submitted in December 2020 and further updated and replaced by a new version in January 2021) Report DSM_EFSA_Calcifediol_CONF_DATA PROT_NEW_0321; Report Annex 1_1A_CONF_DATA PROTECTED_NEW_280121; Report Annex 1_1B_CONF_DATA PROTECTED_NEW_280121; Report Annex 1_2A_CONF_DATA PROTECTED_NEW_280121; Report Annex 1_2B_CONF_DATA PROTECTED_NEW_280121; Report Annex 1_2C_CONF_DATA PROTECTED_NEW_280121; Report Annex 2_CONF_DATA PROTECTED_NEW_280121; Report_Annex I_1 2_CONF_DATA PROT_202103; Report_Annex I_3_CONF_DATA PROT_202103; Report_Annex I_4_CONF_DATA PROT_202103.
([21]) *EFSA Journal* 2021;19(6):6660.

(9) Annex II to Directive 2002/46/EC lists the substances that may be used as forms of vitamins and minerals in the manufacture of food supplements. Article 6(3) of that 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 to enforce compliance with the Article 6(3) of Directive 2002/46/EC. In addition, both Regulation (EU) No 1169/2011 of the European Parliament and of the Council ([22]) and Directive 2002/46/EC provide that the information on vitamins and minerals in a product is to 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 the Authority 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 $D_3$.

(10) On 5 July 2023, the Authority adopted its 'Scientific opinion on the tolerable upper intake level for vitamin D, including the derivation of a conversion factor for calcidiol monohydrate' ([23]). The opinion concerned an updated exposure assessment for vitamin D and proposed a factor of 2,5 for the conversion of calcidiol monohydrate into vitamin $D_3$ for labelling purposes and for doses up to 10 µg/day.

(11) Following that opinion, in accordance with Article 31 of Regulation (EC) No 178/2002 of the European Parliament and of the Council ([24]), the Commission asked the Authority to provide scientific and technical assistance as regards the evaluation of calcidiol monohydrate as a novel food, in particular to reconsider the outcome of the opinion on the safety of calcidiol monohydrate.

(12) On 25 January 2024 the Authority published the scientific and technical report 'Scientific and technical assistance to the evaluation of the safety of calcidiol monohydrate as a novel food' ([25]).

(13) In its report, the Authority concluded that the novel food calcidiol monohydrate proposed for use in food supplements is a bioavailable source of the biologically active metabolite of vitamin D (1,25-dihydroxyvitamin D) and that a conversion factor of 2,5 reflects the relative bioavailability of calcidiol monohydrate as compared to vitamin $D_3$ under the proposed conditions of use and use levels. The Authority further concluded that the novel food calcidiol monohydrate proposed for use in food supplements is safe under the proposed conditions of use and use levels (up to 10 µg/day) for children from 11 years of age and for adults, including pregnant and lactating women, as well as under the proposed conditions of use and use levels (up to 5 µg/day) for children from 3 to 10 years of age.

(14) The opinions and the report of the Authority give sufficient grounds to establish that calcidiol monohydrate when used at levels of up to 10 µg/day in food supplements intended for children from 11 years of age and for adults, including pregnant and lactating women, and when used at levels of up to 5 µg/day in food supplements intended for children from 3 to 10 years of age fulfils the conditions for its placing on the market in accordance with Article 12(1) of Regulation (EU) 2015/2283.

([22]) 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, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004 (OJ L 304, 22.11.2011, p. 18, ELI: http://data.europa.eu/eli/reg/2011/1169/oj).

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

([24]) Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety (OJ L 31, 1.2.2002, p. 1, ELI: http://data.europa.eu/eli/reg/2002/178/oj).

([25]) *EFSA Journal* 2024;22:e8520.

(15) In its 2021 scientific opinion, the Authority noted that 'calcifediol' (calcidiol) is used in the Union as a human medicinal product, approved in the Member States and in some countries outside the Union. Directive 2001/83/EC of the European Parliament and of the Council ([26]) applies where a product, considering all its characteristics, may fall both within the definition of 'medicinal product' as laid down in Article 1(2) of that Directive and within the definition of a 'food' covered by Regulation (EU) 2015/2283. In that respect, where a Member State establishes, in accordance with Directive 2001/83/EC, that a product is a medicinal product, it may restrict the placing on the market of that product as a food in accordance with Union law.

(16) In its 2021 scientific opinion, the Authority noted that its conclusion on the safety of the novel food was based on scientific data from the master data and the product specifications, the studies on absorption, distribution, metabolism and excretion (ADME studies), the toxicity studies, the human studies and the analytical reports, including the annexes, without which it could not have assessed the novel food and reached its conclusion.

(17) The Commission requested the applicant to further clarify the justification provided with regard to their proprietary claim over those studies and to clarify their claim to an exclusive right of reference to them in accordance with Article 26(2), point (b), of Regulation (EU) 2015/2283.

(18) The applicant declared that they held proprietary and exclusive rights of reference for all studies submitted, at the time they submitted the application and therefore third parties could not lawfully access, use or refer to those studies.

(19) The Commission assessed all the information provided by the applicant and considered that they have sufficiently substantiated the fulfilment of the requirements laid down in Article 26(2) of Regulation (EU) 2015/2283. Therefore, the master data for calcidiol; the comparison of 25(OH)D concentration in human serum/plasma following oral supplementation of calcifediol or cholecalciferol; the comparative metabolism of [14C]-calcifediol and [14C]-cholecalciferol following multiple oral administration in the intact male han wistar rat; the comparative metabolism of [14C]-calcifediol and [14C]-cholecalciferol following single oral administration in the bile duct cannulated male han wistar rat; the acute oral toxicity study on calcifediol in rats; the evaluation of the mutagenic activity of D5M0471 17 in an *in vitro* mammalian cell gene mutation test with L5178Y mouse lymphoma cells; the micronucleus test in bone marrow cells of the rat with DSM047117; the *Salmonella typhimurium* and *Escherichia coli* reverse mutation assay; the chromosome aberration test in human lymphocytes *in vitro* with calcifediol; the 90-day oral toxicity study with DSM0471 17 by dietary administration in the rat followed by a 28-day recovery period; the 3-month oral toxicity study with Rovimix® D3-500 by dietary administration followed by a 4-week recovery period in Wistar rats; the dose finding study in physically non-frail and (pre-)frail elderly to measure 25(OH) vitamin D levels after supplementation with HY.D calcifediol 25 SD/S and vitamin $D_3$; the response of serum 25-hydroxyvitamin D to different doses of calcifediol 0,25 SD/S compared to vitamin $D_3$ supplementation: a randomized, controlled, double blind, long term pharmacokinetic study; the report on the particle size distribution and its annexes should be protected in accordance with Article 27(1) of Regulation (EU) 2015/2283. Accordingly, only the applicant should be authorised to place calcidiol monohydrate on the market within the Union during a period of five years from the entry into force of this Regulation.

(20) However, restricting the authorisation of calcidiol monohydrate and the reference to the data contained in the applicant's file for their sole use does not prevent subsequent applicants from applying for an authorisation to place on the market the same novel food provided that their application is based on legally obtained information supporting such an authorisation.

(21) It is appropriate that the inclusion of calcidiol monohydrate as a novel food in the Union list of novel foods contains the information referred to in Article 9(3) of Regulation (EU) 2015/2283. In line with the conditions of use of food supplements containing calcidiol monohydrate as proposed by the applicant and assessed by the Authority, it is necessary to inform the consumers in that regard by appropriate labelling about the uses of food supplements containing calcidiol monohydrate.

([26]) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67, ELI: http://data.europa.eu/eli/dir/2001/83/oj).

(22) Calcidiol monohydrate should be included in the Union list of novel foods set out in Implementing Regulation (EU) 2017/2470. The Annex to Implementing Regulation (EU) 2017/2470 should therefore be amended accordingly.

(23) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Plants, Animals, Food and Feed,

HAS ADOPTED THIS REGULATION:

*Article 1*

1. Calcidiol monohydrate is authorised to be placed on the market within the Union.

Calcidiol monohydrate shall be included in the Union list of novel foods set out in Implementing Regulation (EU) 2017/2470.

2. The Annex to Implementing Regulation (EU) 2017/2470 is amended in accordance with the Annex to this Regulation.

*Article 2*

Only the company DSM Nutritional Products Ltd. ([27]) is authorised to place on the market within the Union the novel food referred to in Article 1, for a period of 5 years from 1 May 2024, unless a subsequent applicant obtains an authorisation for that novel food without reference to the scientific data protected pursuant to Article 3 or with the agreement of DSM Nutritional Products Ltd.

*Article 3*

The scientific data contained in the application file and fulfilling the conditions laid down in Article 26(2) of Regulation (EU) 2015/2283 shall not be used for the benefit of a subsequent applicant for a period of 5 years from the date of entry into force of this Regulation without the agreement of DSM Nutritional Products Ltd.

*Article 4*

This Regulation shall enter into force on the twentieth day following that of its publication in *the Official Journal of the European Union*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 10 April 2024.

*For the Commission*
*The President*
Ursula VON DER LEYEN

([27]) Address: Wurmisweg 576, 4303 Kaiseraugst, Switzerland.

*ANNEX*

The Annex to Implementing Regulation (EU) 2017/2470 is amended as follows:

(1) in Table 1 (**Authorised novel foods**), the following entry is inserted:

| Authorised novel food | Conditions under which the novel food may be used | | Additional specific labelling requirements | Other requirements | Data protection |
|---|---|---|---|---|---|
| '**Calcidiol monohydrate** | *Specified food category* | *Maximum levels* | 1. The designation of the novel food on the labelling of the foodstuffs containing it shall be "calcidiol (calcifediol) monohydrate (vitamin D)".<br><br>2. The labelling of food supplements containing the novel food shall bear a statement that they should not be consumed by infants and children under 3 years of age/children under 11 years of age, depending on the age group the product is intended for. | | Authorised on 1 May 2024. This inclusion is based on proprietary scientific evidence and scientific data protected in accordance with Article 26 of Regulation (EU) 2015/2283.<br><br>Applicant: DSM Nutritional Products Ltd., Wurmisweg 576, 4303 Kaiseraugst, Switzerland. During the period of data protection, the novel food calcidiol monohydrate is authorised for placing on the market within the Union only by DSM Nutritional Products Ltd., unless a subsequent applicant obtains authorisation for the novel food without reference to the proprietary scientific evidence or scientific data protected in accordance with Article 26 of Regulation (EU) 2015/2283 or with the agreement of DSM Nutritional Products Ltd.<br>End date of the date protection: 1 May 2029.' |
| | Food supplements as defined in Directive 2002/46/EC, excluding food supplements for infants and young children | 10 µg/day for children from 11 years of age and adults<br><br>5 µg/day for children from 3 to 10 years of age | | | |

(2) in Table 2 (**Specifications**), the following entry is inserted:

| Authorised Novel Food | Specification |
|---|---|
| '**Calcidiol monohydrate** | **Description/Definition:**<br>The novel food is calcidiol monohydrate (25-hydroxycholecalciferol monohydrate). The novel food contains the monohydrate form of the major circulating metabolite of vitamin $D_3$ in the body and is a source of 1,25-dihydroxyvitamin D, the biologically active form of vitamin D.<br><br>Conversion factor: 1 µg calcidiol = 2,5 µg vitamin $D_3$ for doses up to 10 µg/day. |

| | |
|---|---|
| | The production process of the novel food starts with a yeast fermentation which results in a mixture of sterols, with trienol being the major sterol obtained. After the fermentation, purification and several chemical steps follow. The chemical steps include saponification and extraction, where the trienol is isolated from the biomass. This is followed by a hydroxylation step to separate the trienol from the other sterols. Trienol is then epoxidised and subsequently reduced to give 25-hydroxydehydrocholesterol. A photoreaction follows, to obtain a mixture of 25-hydroxy-previtamin $D_3$, 25-hydroxy-tachysterol and 25-hydroxy-lumisterol. Thereafter, the 25-hydroxy-previtamin $D_3$ is thermally isomerised to "Calcidiol" and recrystallized to obtain the novel food of the required purity.<br><br>The novel food is intended to be placed on the market as a diluted form "0,25 % w/w", containing 0,250-0,275 % w/w of calcidiol (anhydrous). The novel food needs to be placed on the market in a preparation guaranteeing its stability.<br><br>Chemical name according to IUPAC:<br>(1S,3Z)-3-[(*2E*)-2-[(1R,3αS,7αR)-1-[(*2R*)-6-hydroxy-6-methylheptan-2-yl]-7α-methyl-2,3,3α,5,6,7-hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylidenecyclohexan-1-ol; hydrate<br>CAS Number: 63283-36-3 (Calcifediol monohydrate)<br>Empirical formula: $C_{27}H_{44}O_2.H_2O$<br>Molecular weight: 418,7 g/mol<br><br>**Characteristics/composition:**<br>$25(OH)D_3.H_2O$: 97,0-100 %<br>Total related substances: ≤ 1,5 %, of which: $\Delta^{22}$-$25(OH)D_3$: ≤ 0,5 %; Lumisterol [a]: ≤ 0,5 %; pre-$25(OH)D_3$ [b]: ≤ 0,5 %; Tachysterol [c]: ≤ 0,5 %; trans-Vitamin $D_3$ [d]: ≤ 0,5 %<br>Other impurities: ≤ 0,10 %<br>Water content: 3,8-5,0 %<br>Acetone: ≤ 1 000 mg/kg<br>Isopropanol: ≤ 10 mg/kg<br><br>**Heavy metals:**<br>Arsenic: ≤ 1 mg/kg |

([a]) 9b,10a-Cholesta-5,7-diene-3b,25-diol (25(OH)).
([b]) Cholesta-5,7-diene-3b,25-diol.
([c]) (6E)-9,10-Secocholesta-5(10),6,8-triene-3b,25-diol (iso-25(OH)).
([d]) (5E,7E)-9,10-Secocholesta-5,7,10(19)-triene-3b,25-diol.'