Meeting

Magnesium Lthreonate (Magtein®) Discussion Paper

Committee Paper for Discussion - ACNFP/154/03

Advisory Committee For Novel Foods and Processes

Application for Authorisation as a Novel Food for Magnesium Lthreonate (Magtein®).

Application number RP956

Issue

1. An application has been received under the novel food authorisation process (regulation 2015/2283 as repatriated) for magnesium L-threonate monohydrate (Magtein®).

2. The Committee is asked to advise on whether the available data provides an adequate basis for a risk assessment, and whether the novel food is safe and not nutritionally disadvantageous under the proposed use and use levels.

Background

3. On the 7th April 2021, the FSA received the submission for magnesium Lthreonate monohydrate (Magtein®) from AIDP.

4. The novel food ingredient is made by the chemical reaction of ascorbic acid and calcium carbonate to form calcium L-threonate which is then converted by a further reaction to magnesium L-threonate monohydrate. The applicant proposes to use the novel food as magnesium source in food supplements only.

5. The application dossier is attached as Annex A and the annex to the dossier is attached as Annex B. Both annexes contain confidential information.

This application

Identification

6. The novel food, with the trade name Magtein®, corresponds to magnesium L-threonate monohydrate, commonly named magnesium L-threonate, and is composed of 86% to 91% of L-threonic acid and of 7.2% to 8.3% of magnesium. This organic salt is made by the multi-step chemical reaction of ascorbic acid, calcium carbonate and magnesium carbonate. The final composition is verified by titration (Annex B [Annex 35] – **confidential**).

Production Process

7. The initial step in the production process involves the reaction of calcium carbonate with ascorbic acid in deionized water. The further addition of hydrogen peroxide leads to the formation of calcium L-threonate. This solution is filtered and the calcium salt is crystallised.

8. The calcium L-threonate is dissolved in deionized water. Oxalic acid is added and allowed to dissolve before magnesium carbonate is added. A substitution reaction occurs and a calcium oxalate salt precipitates in the solution. This is removed by centrifuge. The remaining aqueous solution of magnesium Lthreonate is neutralised and then decolourised with activated carbon. The carbon is removed by filtration. The filtrate containing magnesium L-threonate is reduced in volume by condensation. Ethanol is added which allows the magnesium salt to crystallise. This solid salt is centrifuged and then oven dried to yield magnesium L-threonate monohydrate.

9. The production method is briefly described (Annex A: p14 – 16 dossier and Annex B [Annex 6]). Additional details on the manufacturing process were provided by the applicant (Annex D, p2 – 3 RFI Letter).

10. The acceptance criteria for the raw materials and processing aids are provided (Annex B [Annex 45]). The applicant confirms that the production facility is registered with the FDA and US state authorities, and the novel food is produced under GMP (Annex B [Annexes 7 – 12]. Further, the applicant has provided justification on the critical point parameters (Annex B [Annex 46]).

Composition and Specification

11. The applicant has reported analytical data for a number of independent batches of magnesium L-threonate. The data indicates that the manufacturing process results in a consistent final ingredient that meets the proposed specifications for the novel ingredient.

12. The applicant reported the content of solvent residues from five batches of novel food. These results confirmed ethanol residues were present and varied from 131 – 148 ppm (Annex A: p31 dossier and Annex B [Annex 20]). Results from three older batches of the novel food reported ethanol residues below the limit of detection of 10 mg/kg (Annex A: p25 dossier and Annex B [Annex 22]). The results from all batches are below the specification limit for ethanol of 5,000 mg/kg in the novel food (Annex B [Annex 16]).

13. The applicant has reported the heavy metal content in eleven batches of the novel food ingredient – five batches from 2019 and three batches each from 2020 and 2021 (see Table 1). These results are below the EU permitted limits for food supplements: cadmium 1.0 mg/kg; lead 3.0 mg/kg; mercury 0.1 mg/kg (Annex A: p26 dossier and Annex B [Annexes 23, 24 and 25]).

Table 1. Heavy metal analysis of Magnesium-L-Threonate

Batch number	Arsenic (ppm)	Mercury (ppm)	Lead (ppm)	Cadmium (ppm)
N°SM-201904112	0.011	0.002	0.042	0.005
N°SM-201904109	0.014	0.007	0.044	0.004
N°SM-201904110	0.012	0.006	0.030	0.008
N°SM-201904111	0.038	0.001	0.036	0.003

N°SM-201904107	0.019	0.033	0.028	0.001
N°SM-202004113	0.047	0.001	0.010	0.001
N°SM-202004114	0.081	0.005	0.020	0.001
N°SM-202004115	0.069	0.008	0.003	0.001
N°SM-202101105	0.009	0.001	0.005	0.001
N°SM-202101106	0.001	0.001	0.006	0.001
N°SM-202101107	0.001	0.001	0.006	0.001

Method; ICP-MS (USP 730>)

Specification levels for arsenic ≤ 1ppm; mercury ≤ 0.1; lead ≤ 0.5 ppm; cadmium ≤ 0.2 ppm

14. The applicant has reported results for the microbial content in twelve batches of the novel food ingredient – five batches from 2019 and the remaining seven batches from 2011 (Annex A: p32 dossier and Annex B [Annex 3, 20 and 24]). The results confirm that total plate count, and yeast and moulds, were below the specification limits of ≤ 3,000 cfu/g and ≤ 100 cfu/g respectively. E. coli was not detected in 1g and Salmonella was not detected in 25g.

15. The applicant states that the content of pesticide residues, mycotoxins, PAH’s, PCB’s and dioxins in magnesium-L-threonate were not assessed because the novel food is a synthetic product (Annex A: p27 dossier).

16. The applicant has reported data on the physico-chemical properties of magnesium-L-threonate (Annex A: p31 – 32 dossier and Annex B [Annexes 3 and 20]) – the first five batches are recent samples and the remaining seven batches are older samples, with limited data (see Table 2). These results confirm that these batches meet the specification limits for the novel food.

Table 3. Compositional analysis for Magtein®

Parameter	SM-201904112	SM-201904109	SM-201904110	SM-201904111	SM-201904107	2010100
Manufacture Date	**4 04 2019**	**30 03 2019**	**11 04 19**	**05 04 19**	**01 04 19**	
Appearance	White powder	White powder	White powder	White powder	White powder	Conforms
Odour and Taste	Conforms	Conforms	Conforms	Conforms	Conforms	NA
Solubility	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Colour of solution	Conforms	Conforms	Conforms	Conforms	Conforms	NA
Bulk density	0.68g/ml	0.72g/ml	0.77g/ml	0.67g/ml	0.68g/ml	NA
	100.0%	100.0%	100.0%	100.0%	100.0%	NA
Particle size						
	25%	31%	30%	30%	32%	NA

Identification	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Loss on drying	0.4%	0.3%	0.2%	0.3%	0.1%	Conforms
Assay	100.6%	100.5%	100.7%	100.6%	100.5%	Conforms
Magnesium	7.7%	7.7%	7.7%	7.7%	7.7%	7.6%
L-Threonate	NA	NA	NA	NA	NA	87.4%
pH	6.3	6.4	6.4	6.4	6.4	NA

Parameter	**20120208**	**20120301**	**20120402**	**20120502**	**20120506**	**20120603**
Manufacture Date						
Appearance	NA	NA	NA	NA	NA	NA
Odour and Taste	NA	NA	NA	NA	NA	NA
Solubility	NA	NA	NA	NA	NA	NA
Colour of solution	NA	NA	NA	NA	NA	NA

Bulk density	NA	NA	NA	NA	NA	NA
Particle size	NA	NA	NA	NA	NA	NA
Identification	NA	NA	NA	NA	NA	NA
Loss on drying	NA	NA	NA	NA	NA	NA
Assay	NA	NA	NA	NA	NA	NA
Magnesium	7.63%	7.54%	7.65%	7.74%	7.80%	7.84%
L-Threonate	88.8%	88.8%	89.1%	88.2%	87.7%	86.3%
pH	NA	NA	NA	NA	NA	NA

NA – not available

Stability

17. The applicant reports the results from an internal stability study concerning one batch of capsules containing the novel food (Annex A: Table 6, p33 dossier). This trial over 25 months at room temperature assessed the % content of magnesium and L-threonate only (Annex B [Annex 37] – **confidential**). Results for a further four batches covering different time periods, but using the same parameters, were reported by the applicant in response to the RFI letter (p5, Annex D).

18. The stability of three batches of the novel food were assessed for 36 months in a real-time stability study at 25 +/- 2^{o}C and for 6 months in an accelerated stability study (Annex B [Annex 34]). Data concerning the physicochemical properties, biochemical properties and microbiological properties were reported.

The applicant states that the results meet the specification limits and demonstrate the novel food is stable under these conditions (Annex A: Table 7, p34 dossier).

19. Stability data for a further two batches of the novel food covering a time period of 36 months were provided by the applicant, however, the environmental conditions were not defined (Annex D, p6 RFI Letter). The data shows that magnesium-L-threonate is stable over this time period in terms of the physicochemical, biochemical and microbiological properties which meet the specification limits (Annex B [Annex 55]).

Specification

20. The specification parameters for the novel food were assessed using internationally recognised methods or are otherwise determined using internally developed and validated methods (Annex A: p36 dossier and Annex B [Annex 2]).

Table 4. Specification of Magtein®

Parameter	Specification	Method
Appearance	White powder	Visual
Odor and Taste	Characteristic	Organoleptic
Solubility	Water soluble	Visual (1% at 25°C)
Color of solution	Clear	Visual (1% solution)
Bulk density	> 0.4 g/cc	Loose fill in graduated cylinder
Particle size	NLT 90% thru a US # 20 MMT 60% thru a US # 200	Ro Tap (3 min.) Ro Tap (3 min.)
Identification	Conforms to standard	FTIR

Loss on drying	≤5.0%	105°C, 4 hours
Assay	98-102%	Titration
Magnesium	7.2 to 8.3% (mg/g)	ICP-OES / (AOAC 984.27 mod, 927.02 mod, 985.01 mod, 965.17 mod)
L-Threonate	82 to 91%	HPLC
Residual solvents (Ethanol)	≤5000 ppm	USP 467
pH	5.8 - 7.0	USP (1% in H20)
Arsenic	≤1 ppm	ICP/MS USP 730
Mercury	≤0.1 ppm	ICP/MS USP 730
Lead	≤0.5 ppm	ICP/MS USP 730
Cadmium	≤0.2 ppm	ICP/MS USP 730
Total plate count	≤3000 CFU/g	USP 2021>

Yeast and mold	≤100 CFU/g	USP 2021>
E. coli	Negative/1g	USP 2022>
Salmonella	Negative/25g	USP 2022>

History of Use

21. The closely related compound, calcium L-threonate, was authorised by EFSA in 2008 as a source of calcium (Annex A: p38 dossier). The EFSA Panel stated that at the intended use level of 400mg calcium and 2700mg L-threonate per day there were no safety concerns.

22. The applicant states that the novel food has no history of use in the EU. However, magnesium L-threonate is recognised as GRAS ingredient in the USA and is also approved in Canada with a health claim as a dietary supplement (Annex A: p39 dossier).

Proposed Use and Intake

23. The applicant states that the novel food is intended to be used by adults in general population, but this does not include vulnerable groups such as children, pregnant or lactating women (Annex A: p40 dossier).

24. The novel food is intended to replace other sources of magnesium as or in food supplements only, but is not intended to be used in addition to other sources of magnesium (Annex A: p40 dossier).

25. The applicant states that the maximum dose of magnesium L-threonate will be 3 g/day which provides up to 249 mg/day of magnesium and up to 2730 mg/day of L-threonate. This complies with the EFSA tolerable upper daily intake level (UL) of 250 mg/day for magnesium from dissociable magnesium salts (Annex A: p40 and p43 dossier). *The Secretariat notes that the UL does not include magnesium naturally present in foods and beverages*.

26. The applicant reports that EFSA have set adequate intake values (level assumed to be adequate for the population’s need) for magnesium in men and women at 350 and 300 mg/day respectively. This is based on the consumption of

different food groups that contribute to the intake of magnesium in the diet (Annex A: p42 dossier). However, the applicant also notes that the daily reference intake/nutrient reference value (NRV) for magnesium is reported as 375 mg/day (Annex A: p37 dossier). *The Secretariat notes this NRV value is defined in Regulation (EU) 1169/2011 (Annex XIII, Table 3).*

27. Estimates of the highest intakes for magnesium (97.5th percentile) plus the maximum intake level for the novel food range from 599 to 877 mg/day. This exceeds the adequate intake value for magnesium of 350 and 300 mg/day for men and women respectively. The applicant states that since the bioavailability of magnesium from food sources is low, these calculated values for magnesium exposure should be treated with caution (Annex A: p42 dossier).

28. The applicant reports that this combined intake for L-threonate is not expected to be a cause for concern given the summary opinion by the EFSA Panel for calcium L-threonate, however, the use of different food supplements containing L-threonate should be contraindicated (Annex A: p43 dossier).

Absorption, Distribution, Metabolism and Excretion (ADME)

29. A dissociation study of magnesium L-threonate conducted at different pH levels demonstrated that magnesium ions and L-threonate ions were detected at pH 2 by ICP-MS and HPLC-MS respectively (Annex B [Annex 36]). The applicant concludes that this data supports the dissociation of magnesium-Lthreonate in gastric fluids to magnesium and L-threonate ions (Annex A: p44 dossier) resulting in the absorption and distribution of the novel food in consumers.

30. The applicant provided a review of a published study by Wang et al (2011) concerning the pharmacokinetics of L-threonate in humans following administration of different doses of calcium L-threonate (Annex A: p44 – 46 dossier). The results confirm that L-threonate is absorbed following ingestion by the test subjects.

31. The applicant reports the results from an unpublished study on the bioavailability of magnesium L-threonate which established that the novel food ingredient has a higher absorption and retention than other sources of magnesium (p46 – 48 dossier). The study report can be found in Annex B [Annex 37] – **confidential**. See also Annex B [Annexes 56 and 57] which show the raw data for figures 2 and 4 in this same report.

32. The applicant provided additional supporting evidence from a published study (Slutsky et al, 2010) on the accumulation of magnesium in CSF in SD rats following the administration of different magnesium salts (Annex A: p48 – 49 dossier).

33. A prospective, randomized, double-blind, placebo-controlled, parallel-group clinical trial conducted by Liu et al (2016) examined the body magnesium status over a 12 week period following supplementation with the novel food ingredient (Annex A: p49 – 50 dossier and Annex B [Annexes 43 and 44]). The results confirmed that magnesium is absorbed following the ingestion of magnesiumL-threonate in humans.

Nutritional Information

34. No nutritional analysis has been performed because L-threonic acid represents not less than 85% and up to 91% of the product and magnesium represents between 7.2% and 8.3% of the product (Annex A: p51 dossier). The applicant suggests that a nutritional analysis would not provide an additional dataset to consider nutritional disadvantage.

Toxicological Information

35. The applicant reports that results from a bacterial reverse mutation assay (OECD TG 471) show that magnesium L-threonate monohydrate is nonmutagenic at concentrations up to 5,000 µg/plate, in the absence or presence of metabolic activation (Annex A: p52 – 53 dossier). The full study report is available in Annex B [Annex 38 – confidential].

36. The applicant reports that results from an *in vivo* murine cell micronucleus test (OECD TG 474) using magnesium L-threonate monohydrate once daily for two days did not induce the formation of micronucleated polychromatic erythrocytes (MNPCE) in the bone marrow of Swiss albino mice at the dose of 2000 mg/kg b.w. (Annex A: p53 – 54 dossier). The full study report is available in Annex B [Annex 39 – confidential].

37. The applicant stated that the selection of the *in vivo* cell micronucleus test rather than the in vitro cell micronucleus test was a requirement of the GRAS safety review undertaken on magnesium-L-threonate (Annex D, p9 RFI Letter).

38. The applicant reports the results from an acute toxicology study, with no guidelines referenced (Annex A: p54 – 55 dossier and Annex B [Annex 40]). The

study concludes that the LD50 for female mice and male mice is 12600 mg/kg and 9260 mg/kg respectively.

39. The applicant reports the results from a 90-day feeding study in rats (OECD TG 408) conducted to GLP principles. The magnesium L-threonate monohydrate was reported to be well tolerated at doses up to 2,000 mg/kg body weight/day (Annex A: p55 – 64 dossier). The full study report is available in Annex B [Annexes 41 and 42 – confidential].

40. The applicant has reported the results from a clinical study evaluating the effects of the novel food in humans at 1.5 g/day and 2.0 g/day (Annex A: p66 – 70 dossier). The report concludes that no adverse effect related safety concerns were raised during these trials (Annex B [Annexes 43 and 44]).

41. The applicant has reviewed the literature concerning the toxicology of magnesium, L-threonate, and the closely related compound, calcium Lthreonate (Annex A: p71 – 74 dossier), which is used to support the safety assessment of novel food ingredient.

42. Further justification for setting the anticipated intake level of magnesium Lthreonate monohydrate (Magtein®) at 3,000 mg/day is provided in response to the RFI letter (Annex D, p10 – 12). The applicant refers to the fact that Lthreonate is endogenous and magnesium is an essential mineral, the conclusion of the GRAS Panel (Annex 3), the level of magnesium is below the EFSA upper tolerable limit for this mineral, the level of L-threonate in the novel food is comparable to the content in calcium-L-threonate in the EFSA summary opinion, and the dose is below the 4,000 mg/day in supplements marketed in Canada and the USA.

Allergenicity

43. The applicant states that the novel food contains magnesium and L-threonic acid only. No protein enters the composition and there no other well-known allergens present. Therefore, the applicant expects there is a low risk of allergenicity (Annex A: p75 dossier).

Committee Action Required

- The Committee is asked whether the available data provide a satisfactory basis for evaluating the safety of this novel food.

- If so the Committee is asked whether it is content to recommend approval of the novel food as an ingredient to be added to the range of foods specified.
- If not, the Committee is asked to indicate what additional data would be required.

Annexes

ACNFP-154-03-Annex A – Dossier [Confidential]

ACNFP-154-03-Annex B – Annexes and References [Confidential]

ACNFP-154-03-Annex C – Request For Information

ACNFP-154-03-Annex D – Applicant’s Response to Request For Information