Safety Assessment: Magnesium L-threonate as a novel food for use in food supplements

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Author: Matt Hall

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Executive Summary

An application was submitted to the Food Standards Agency (FSA) and Food Standards Scotland (FSS) in April 2021 from AIDP, USA ("the applicant") for the authorisation of magnesium L-threonate monohydrate as a novel food.

The novel food is magnesium L-threonate monohydrate which is intended to be used as a source of magnesium in food supplements. Magnesium L-threonate monohydrate is manufactured via a chemical synthetic process, isolated, purified and then dried to a powder.

This new application is seeking to use the novel food within the food category: food supplement.

To support the FSA and FSS in their evaluation of the application, the Advisory Committee on Novel Foods and Processes (ACNFP) were asked to review the safety dossier and supplementary information provided by the applicant. Please note the Committee did not consider any potential health benefits or claims arising from consuming the food, as the focus of the novel food assessment is to ensure the food is safe, and not putting consumers at a nutritional disadvantage.

The FSA and FSS concluded that the applicant had provided sufficient information to assure the novel food, magnesium L-threonate monohydrate, was safe under the proposed conditions of use. The anticipated intake levels and the proposed use in food supplements was not considered to be nutritionally disadvantageous.

The views of the ACNFP have been taken into account in the regulatory assessment which represents the opinion of the FSA and FSS.

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Abbreviations

Acronym	**Definition**
ACNFP	Advisory Committee on Novel Foods and Processes
ADME	Absorption, Distribution, Metabolism and Excretion
AOCS	American Oil Chemists' Society
BW	body weight
CAS	Chemical Abstracts Service
CFU	Colony Forming Unit
cGMP	Current Good Manufacturing Practice
EC	European Commission
EFSA	European Food Safety Agency
EU	European Union
FDA	Food and Drug Administration
FTIR	Fourier Transform Infrared Spectroscopy
g/cc	grams per cubic centimetre
GC-FID	Gas chromatography with flame ionisation detection
GLP	Good Laboratory Practice
HACCP	Hazards Analysis and Critical Control Points

Acronym	Definition
HPLC	High Performance Liquid Chromatography
ICP-MS	Inductively coupled plasma mass spectrometry
ICP-OES	Inductively coupled plasma optical emission spectroscopy
ISO	International Organisation for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
KOH	Potassium hydroxide
ND	not determined
NLT	not less than
NMT	not more than
NOAEL	No Observable Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
ppm	parts per million
SACN	Scientific Advisory Committee on Nutrition
USP	United States Pharmacopoeia

1. Introduction

1. In April 2021, AIDP, USA ("the applicant") submitted a full novel food application for the authorisation of magnesium L-threonate monohydrate. The novel food is a water soluble white to off-white powder which is manufactured via a chemical synthetic process. Magnesium L-threonate monohydrate is intended to be used as a source of magnesium in food supplements.

2. The FSA and FSS have undertaken a safety assessment for magnesium L-threonate monohydrate under the novel foods legislation, assimilated Regulation (EU) 2015/2283. To support the safety assessment, the ACNFP provided the advice outlined in this opinion to the FSA and FSS.

3. The evaluation by the ACNFP assessed the food safety risks of the novel food and its production, in line with Article 7 of assimilated Commission Implementing Regulation (EU) 2017/2469. The regulatory framework and the technical guidance put in place by the European Food Safety Agency (EFSA) for full novel food applications is retained as the basis and structure for the assessment (EFSA NDA Panel, 2021).

4. Following the review by the ACNFP in September 2022, further information was requested from the applicant concerning the identity of the novel food, the production process, the proposed uses, ADME and nutritional information on magnesium L-threonate monohydrate, in order to address information gaps in the initial dossier. The final advice from the Committee was agreed at the 162nd meeting, allowing the FSA and FSS to complete the risk assessment.

5. The document outlines the conclusions of the FSA and FSS on the safety of magnesium L-threonate monohydrate as a novel food.

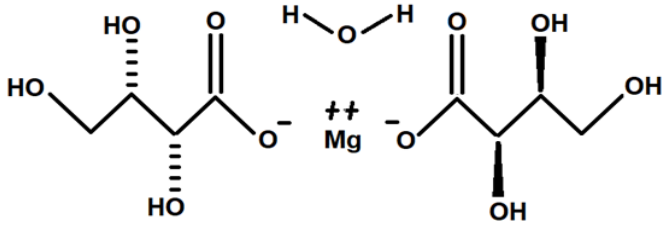
2. Assessment

2.1 Identity of the novel food

6. The novel food, magnesium L-threonate monohydrate (Diagram 1), is classified as a purified chemical substance and characterised by the following information:

IUPAC name	Magnesium (2*R*,3*S*)-2,3,4-trihydroxybutanoate monohydrate
CAS number	500304-76-7
Molecular weight	312.51 g/mol
Molecular formula	$C_8H_{16}MgO_{11}$

Figure 1: The structural formula of magnesium L-threonate monohydrate



7. Magnesium L-threonate monohydrate is a water soluble white to off-white powder which is manufactured via a chemical synthetic process. The content of the novel food is 98 – 102% magnesium L-threonate monohydrate.

8. Confirmation to support the identification of the novel food as magnesium L-threonate monohydrate was provided by elemental analysis, inductively coupled plasma optical emission spectroscopy (ICP-OES) and high-performance liquid chromatography (HPLC).

9. Fourier Transform infrared spectroscopy (FT-IR) analysis ensures that the novel food is magnesium L-threonate monohydrate.

10. Information to support this characterisation was provided for five batches of magnesium L-threonate monohydrate.

2.2 Production Process

11. The production process for magnesium L-threonate monohydrate is a two-step chemical synthetic process. In the first step, ascorbic acid and calcium carbonate are reacted in the presence of hydrogen peroxide to the form calcium L-threonate as an intermediate.

12. In the second step, the calcium in the calcium L-threonate is replaced with magnesium by the addition of magnesium carbonate and oxalic acid.

13. The crude product is then isolated, purified, and dried to a powder to yield magnesium L-threonate monohydrate.

14. Information on the acceptance criteria for the raw materials and processing aids was provided. The purity criteria for the reagents used in the manufacture of magnesium L-threonate monohydrate are listed in Table 1.

Table 1: Purity criteria for reagents used to synthesize the novel food

Raw material	**Purity**
Calcium carbonate	≥ 98%
Ascorbic acid	≥ 99%
Hydrogen peroxide, aqueous	≥ 27.5%
Hydrated basic magnesium carbonate, heavy	40 – 44% magnesium oxide by assay *
Oxalic acid	≥ 99.6%

* Complies with European Pharmacopoeia

15. The manufacturing plant is registered with Food and Drug Administration (FDA) and Californian state authorities. The novel food is produced in compliance with current Good Manufacturing Practice (cGMP) and implements Hazard Analysis and Critical Control Point (HACCP) principles.

16. The presence of oxalic acid residues in the novel food are controlled by monitoring the pH of the reaction solution and ensuring that the content of oxalic acid does not exceed the critical limit of 0.5% for each batch of magnesium L-threonate monohydrate.

17. The production process has characterised the potential hazards and the corresponding control measures are appropriate.

2.3 Compositional information

18. Results from five independent batches of magnesium L-threonate monohydrate demonstrated that the novel food consistently meets the specification levels (Table 2).

Table 2. Compositional Analysis of the novel food

Test Parameter	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Appearance	Conforms	Conforms	Conforms	Conforms	Conforms
Odour and Taste	Conforms	Conforms	Conforms	Conforms	Conforms
Solubility	Conforms	Conforms	Conforms	Conforms	Conforms
Colour of solution	Conforms	Conforms	Conforms	Conforms	Conforms
Bulk density (g/ml)	0.68	0.72	0.77	0.67	0.68
Particle size NLT 90% thru a US # 20 NMT 60% thru a US # 200	 100.0% 25%	 100.0% 31%	 100.0% 30%	 100.0% 30%	 100.0% 32%
Identification	Conforms	Conforms	Conforms	Conforms	Conforms
Loss on drying (%)	0.4	0.3	0.2	0.3	0.1
Assay (%)	100.6	100.5	100.7	100.6	100.5
Magnesium (%)	7.7	7.7	7.7	7.7	7.7
L-Threonate (%)	ND	ND	ND	ND	ND

Test Parameter	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Ethanol residues (ppm)	6	138	148	147	131
pH [USP (1% in H_2O)]	6.3	6.4	6.4	6.4	6.4
Arsenic (ppm)	0.011	0.014	0.012	0.03	0.019
Mercury (ppm)	0.002	0.007	0.006	0.001	0.0033
Lead (ppm)	0.042	0.044	0.030	0.036	0.028
Cadmium (ppm)	0.005	0.004	0.008	0.003	< 0.001
Total plate count (CFU/g)	10	10	10	< 10	10
Yeast and mould (CFU/g)	10	< 10	< 10	< 10	< 10
E. coli (Absent in 1g)	Absent	Absent	Absent	Absent	Absent
Salmonella (Absent in 25g)	Absent	Absent	Absent	Absent	Absent

Assay = [(% magnesium + % threonate) x (312.51 / 294.50)] + % water

NLT = not less than; NMT = not more than; ND = not determined; ppm = parts per million; CFU = colony forming units

19. The assay calculation for magnesium L-threonate monohydrate requires three parameters: magnesium, L-threonate and loss on drying content. As the L-threonate content was not provided (Table 2), further analytical data was requested for magnesium, L-threonate monohydrate and loss on drying (Table 3).

Table 3. Magnesium, L-threonate and loss on drying content for magnesium L-threonate monohydrate

Test Parameter	Batch 6	Batch 7	Batch 8
Magnesium (%)	7.7%	7.8%	7.8%
L-threonate (%)	85.4%	86.2%	85.3%
Loss on drying (%)	0.2%	0.2%	0.2%
Assay (%)	99.0%	100.0%	99.0%

Assay = [(% magnesium + % threonate) x (312.51 / 294.50)] + % water

20. An assessment was conducted in accordance with the EFSA Guidance on technical requirements for regulated food and feed product applications (EFSA, 2021) to establish the presence of small particles including nanoparticles in the novel food. A water solubility test, following OECD TG 105 guidelines, confirmed that the novel food exceeded the decision criteria for solubility (> 33.3 g/L), as described in the guidance. Therefore, further evaluation for the presence of nanoparticles in magnesium L-threonate monohydrate is not required.

21. Certification was provided to demonstrate that the contract laboratories were accredited to perform these analytical studies. Where in-house analysis was utilised, full methodology and supporting validation documentation was provided.

22. The data presented indicate the novel food can be consistently produced within the proposed specification.

2.4 Stability

23. Three batches of magnesium L-threonate monohydrate were assessed in a real-time stability study at 25 +/- 2°C for 36 months and a 6-month accelerated stability study. The physicochemical, biochemical, and microbiological parameters complied with the novel food specification limits confirming magnesium L-threonate monohydrate is stable under these conditions.

24. An additional 36-month real-time stability study for two batches of magnesium L-threonate monohydrate, following the same parameters, confirmed the novel food is stable under these conditions.

25. The data provided supports the stability of the novel food for up to 36 months.

2.5 Specification

26. The specification parameters for the novel food (Table 4) were assessed using internationally recognised methods or are otherwise determined using internally developed and validated methods.

Table 4: Specification for magnesium L-threonate monohydrate

Parameter	Specification	Method
Appearance	White powder	Visual
Odour and Taste	Characteristic	Organoleptic
Solubility	Water soluble	Visual (1% at 25°C)
Colour of solution	Clear	Visual (1% solution)
Bulk density	> 0.4 g/ml	Loose fill in graduated cylinder
Particle size	NLT 90% thru a US # 20 MMT 60% thru a US # 200	Ro Tap sieve shaker (3 min.) Ro Tap sieve shaker (3 min.)
Identification	Conforms to standard	FTIR
Loss on drying	≤ 5.0%	105°C, 4 hours
Assay	98-102%	Calculation
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
Ethanol residues	≤ 5000 ppm	USP 467
pH	5.8 – 7.0	USP (1% in H_2O)
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 mould	≤ 100 CFU/g	USP <2021>
E. coli	Absent in 1g	USP <2022>
Salmonella	Absent in 25g	USP <2022>

NLT = not less than; NMT = not more than; ND = not determined; ppm = parts per million; CFU = colony forming units

27. Oxalic acid, which is used as a reagent in this production process, was detected at 0.155% w/w in magnesium L-threonate monohydrate.

28. Oxalic acid is an antinutrient which can adversely affect the body's ability to handle essential minerals such as iron, magnesium and especially calcium. In particular, calcium oxalate can form and precipitate in the kidneys and bladder leading to the development of kidney and bladder stones. The addition of a maximum specified limit for oxalic acid/oxalate content in the novel food is recommended as a risk management measure.

29. The information provided is sufficient for the specification of magnesium L-threonate monohydrate, and appropriately characterises the novel food seeking authorisation.

2.6 History of Use

30. Magnesium is recognised as an essential mineral which has a key role in many physiological processes (EFSA, 2016). L-threonate is a recognised metabolite of ascorbic acid and is also an endogenous compound in the body (EFSA, 2008).

31. The novel food has no history of use in the EU. However, calcium L-threonate, the production intermediate of magnesium L-threonate monohydrate, is authorised as a source of calcium (EFSA, 2008).

32. Magnesium L-threonate monohydrate is recognised as a GRAS ingredient in the USA and is also approved in Canada with a health claim as a dietary supplement.

33. The history of use does not indicate any further areas for evaluation.

2.7 Proposed Use and Anticipated Intake

34. Magnesium L-threonate monohydrate is intended to be used by the adults only to replace other sources of magnesium in food supplements. The novel food is not intended to be used in addition to other sources of magnesium.

35. The maximum dose of the novel food is 3,000 mg/day, which will provide up to 249 mg/day of magnesium and up to 2,730 mg/day of L-threonate.

36. The tolerable upper intake level for magnesium from readily dissociable magnesium salts (e.g., chloride, sulphate, aspartate, lactate), used in food supplements or added to foods, is 250 mg/day (EFSA, 2015).

37. Dietary surveys report that the estimated mean and high-level intakes (97.5th percentile) for magnesium from dietary sources range from 208 – 327 mg/day and 350 – 628 mg/day, respectively (EFSA, 2006). By comparison, the adequate intake[1] values for magnesium in men and women are reported as 350 and 300 mg/day, respectively (EFSA, 2015).

38. Magnesium is typically bound or chelated (e.g. chlorophyll; phosphate; phytate) in food and beverages. Consequently, consumer intake levels from dietary sources of magnesium are expected to be limited due to the low bioavailability of the mineral (EFSA, 2006).

39. L-threonate is not typically consumed as a food. In the previous safety assessment of calcium L-threonate as a source of calcium (EFSA, 2008), the margin of safety was considered sufficiently large given that L-threonate is an endogenous compound in the body. Since the levels of L-threonate in the novel food are comparable, this is not expected to be a cause for concern for consumers of magnesium L-threonate monohydrate. However, the consumption

[1] Adequate intake is the average nutrient level consumed daily by a typical healthy population that is assumed to be adequate for the population's needs.

of calcium L-threonate and magnesium L-threonate monohydrate on the same day should be contraindicated.

2.8 Absorption, Distribution, Metabolism and Excretion (ADME)

38. Active transport systems tightly control the amount of magnesium that crosses from the digestive tract into the bloodstream. Therefore, the absorption of magnesium from the novel food requires magnesium L-threonate monohydrate to be a dissociable salt under physiological conditions in the gastrointestinal tract. Patel, (2020) [unpublished paper] demonstrated that magnesium L-threonate monohydrate can dissociate under acidic conditions (pH 2) to magnesium ions and L-threonate ions, albeit not under neutral conditions.

39. The absorption of magnesium from the novel food has been confirmed by Liu *et al.* (2016). A prospective, randomised, double-blind, placebo-controlled, parallel-group clinical trial examining serum magnesium levels over a 12-week period following supplementation with magnesium-L-threonate monohydrate reported that magnesium is absorbed following the ingestion of novel food in humans.

40. A study in Sprague-Dawley rats established that approximately 60% of the magnesium L-threonate dose is absorbed compared to approximately 40% for magnesium chloride, magnesium citrate or magnesium gluconate (Slutsky *et al.*, 2010). A more recent study in rats confirmed that magnesium L-threonate has a higher absorption than magnesium chloride and magnesium sulphate (Sadir *et al.*, 2019).

41. The ADME of magnesium L-threonate monohydrate does not indicate any further areas for concern.

2.9 Nutritional information

42. The novel food is magnesium L-threonate monohydrate which is specified at 82 – 91% L-threonate and 7.2 – 8.3% magnesium by weight.

43. The maximum dose level for the novel food is comparable to the upper tolerable daily intake value for magnesium. Reports have suggested that magnesium is “the natural calcium antagonist” which can inhibit calcium enteral absorption (EFSA, 2006). Spencer et al. (1994) reported that magnesium intakes of 576 mg/day had no impact on the calcium levels in human volunteers. The Expert Group on Vitamins and Minerals stated that based on a majority of studies, 400 mg/day of magnesium supplements would not be expected to result in any significant adverse effects (EVM, 2003). Therefore, the evidence that magnesium has a negative influence on the serum calcium levels under physiological conditions was considered to be weak (EFSA, 2006).

44. Oxalic acid is a reactant in the novel food production process. Analysis from one batch of the novel food demonstrated that residues of this substance were present at 0.155% w/w. Given that the maximum intake for magnesium L-threonate monohydrate is 3,000 mg/day, this would provide a daily dose of oxalic acid equivalent to 4.65 mg/day.

45. Holmes and Kennedy (2000) reported that oxalic acid exposure levels from a small sample of consumers ranged from 44 to 352 mg/day (mean intake of 152 mg/day). Noonan and Savage (1999) calculated mean exposure levels to oxalic acid in the English diet as 70 – 150 mg/day.

46. Based on this information, the consumption of the novel food as a source of magnesium is not expected to be nutritionally disadvantageous for consumers at the maximum use levels specified in this application.

2.10 Toxicological information

47. Toxicological studies were performed with magnesium L-threonate monohydrate to support the safety assessment of the novel food. The respective study reports are unpublished and claimed as proprietary data. They were reviewed by the ACNFP and considered essential in the assessment of the safety of the novel food.

2.10.1 Genotoxicity

48. *In vitro* genotoxicity testing of magnesium L-threonate monohydrate was conducted under Good Laboratory Practice (GLP) conditions and according to the OECD guidelines: *in vitro* bacterial reverse mutation test (OECD TG 471) and *in vivo* mammalian erythrocyte micronucleus test (OECD TG 474). This is not the approach recommended by the UK Committee on Mutagenicity or in the guidance on the preparation and submission of an application for authorisation of a novel food in the context of assimilated Regulation (EU) 2015/2283.

49. The Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment (EFSA, 2011) recommends two *in vitro* tests as the first step in testing for genotoxicity: *in vitro* bacterial reverse mutation test (OECD TG 471) and *in vitro* mammalian cell micronucleus test (OECD TG 487). This approach addresses the key endpoints for adequately assessing genotoxicity with the minimum number of tests and avoiding unnecessary animal tests.

50. The *in vivo* mammalian erythrocyte micronucleus test assesses both structural and numerical chromosomal aberrations and is an appropriate follow-up test for *in vitro* clastogens and aneugens. Therefore, this *in vivo* test, which is valid because the ADME data confirms the bone marrow cells are exposed to the novel food, along with the *in vitro* bacterial reverse mutation test, provide assurance that the genotoxicity of the novel food has been adequately assessed.

51. The *in vitro* bacterial reverse mutation test (Harke, 2020 [unpublished]) demonstrated that magnesium L-threonate monohydrate is non-mutagenic, in the absence or presence of metabolic activation.

52. The *in vivo* mammalian erythrocyte micronucleus test (Sai Kumar, 2021 [unpublished]) demonstrated that magnesium L-threonate monohydrate is non-clastogenic and non-aneugenic.

53. The results from these *in vitro* and *in vivo* studies support the conclusion that the novel food is not genotoxic.

2.10.2 Sub-chronic toxicity

54. A Repeated Dose 90-Day Oral Toxicity Study in Rodents (Saravanan, 2021 [unpublished]) was conducted under GLP conditions according to OECD TG 408 guidelines as recommended by the Guidance on the preparation and submission of an application for authorisation of a novel food in the context of assimilated Regulation (EU) 2015/2283. The aim of the study was to identify any adverse effects following the consumption of magnesium-L-threonate monohydrate.

55. In this 90-day feeding study, each group consisted of 10 female and 10 male Sprague Dawley rats which were fed 0 (control – vehicle only [water]), 500, 1,000 or 2,000 mg/kg BW/day of magnesium-L-threonate monohydrate by oral gavage. Additionally, satellite groups consisting of 6 female rats and 6 male rats for the control and high dose treatment were used as recovery groups.

56. No deaths, test item-related clinical abnormalities, ocular changes, or differences in food consumption and bodyweight between test groups were reported. In addition, there were no statistically significant dose dependent changes in haematology, clinical chemistry, serum hormone levels, urinalysis, or organ weights.

57. No dose related abnormalities were noted during the necropsy or histopathological evaluation. Therefore, the no observable adverse effect level (NOAEL) for magnesium-L-threonate monohydrate was considered to be the highest dose tested of 2,000 mg/kg BW/day.

2.10.3 Human studies

58. A prospective, randomized, double-blind, placebo-controlled, parallel-group clinical trial following fifty male and female adults (aged 50 – 70 years old) for 12 weeks was conducted (Liu *et al.*, 2016). Doses of 1.5 g/day were given to the participants who weighed under 70kg, and doses of 2.0 g/day were given to those who weighed 70 – 100kg. No adverse effect related safety concerns were reported during the trial.

2.11 Allergenicity

59. Magnesium L-threonate monohydrate is a chemically purified substance which is not expected to produce an IgE-mediated allergenic response in consumers.

3. Discussion

60. The novel food is magnesium L-threonate monohydrate, which consists of 7.2 – 8.3% w/w magnesium, 82 – 91% w/w L-threonate and ≤ 5% w/w water.

61. Magnesium L-threonate monohydrate is manufactured by a two-step chemical synthetic process to yield a water soluble white to off-white powder with a purity of 98 – 102%.

62. Magnesium L-threonate monohydrate is intended to be used as a source of magnesium and is proposed to replace other sources of magnesium in food supplements only. The novel food is not intended to be used in addition to other sources of magnesium. The maximum dose of magnesium L-threonate monohydrate is 3,000 mg/day which provides up to 249 mg/day of magnesium and up to 2,730 mg/day of L-threonate.

63. The NOAEL for the magnesium L-threonate monohydrate in the sub-chronic rat study is 2,000 mg/kg BW/day.

64. The exposure to magnesium L-threonate monohydrate on a body weight basis for consumers over 18 years is 39.5 – 42.1 mg/kg BW/day. These values were derived from the maximum dose of 3,000 mg/day and the default bodyweights for the adult, the elderly, and the very elderly sub-populations of 73.9 kg, 76.0 kg and 71.2 kg, respectively (EFSA, 2012).

65. The Margin of Safety (MoS) for the novel food was calculated by comparing the NOAEL for the magnesium L-threonate monohydrate (2,000 mg/kg BW/day) with the exposure of magnesium L-threonate monohydrate on a body weight basis (39.5 – 42.1 mg/kg BW/day). The resulting MoS for magnesium L-threonate monohydrate ranges from 48 to 51 in these sub-populations.

66. The estimated mean and high-level intakes (97.5th percentile) for magnesium from dietary sources range from 208 – 327 mg/day and 350 – 628 mg/day,

respectively (EFSA, 2006). However, the magnesium in foods and beverages is typically bound or chelated, which accounts for the low bioavailability of this mineral from dietary sources.

67. The maximum daily dose of the novel food could provide up to 249 mg/day of magnesium. Animal studies indicate that the absorption of magnesium from the novel food, although reportedly higher compared to other dissociable magnesium salts, is not 100% of the dose. Therefore, consumer exposure levels to magnesium from the novel food are expected to be lower than the tolerable upper limit for magnesium of 250 mg/day.

4. Conclusion

68. The FSA and FSS have undertaken the assessment of magnesium L-threonate monohydrate and concluded that the novel food is safe under the proposed conditions of use and does not pose a safety risk to human health. The anticipated intake levels and the proposed use was not considered to be nutritionally disadvantageous.

69. These conclusions were based on the information in the novel food dossier submitted by the applicant plus the supplementary information and could not have been reached without the following data claimed as proprietary by the applicant:

    - bioavailability study (Zhao *et al.* [unpublished]); *in vitro* bacterial reverse mutation test (Harke, 2020 [unpublished]), *in vivo* micronucleus test (Sai Kumar, 2021 [unpublished]); 90-day repeat dose feeding study with the novel food (Saravanan, 2021 [unpublished]) and double-blind human clinical trial (Krieger et al., 2013 [unpublished]

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