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SCIENTIFIC OPINION

Safety of magnesium L-threonate as a novel food pursuant to regulation (EU) 2015/2283 and bioavailability of magnesium from this source in the context of Directive 2002/46/EC

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Abstract

Following a request from the European Commission, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on the safety of magnesium L-threonate as a novel food (NF) pursuant to Regulation (EU) 2015/2283 and to address the bioavailability of magnesium from this source in the context of Directive 2002/46/EC. The NF, produced by chemical synthesis, is intended to be used as new source for magnesium in food supplements at a maximum intake level of 3000 mg per day by adults, except for pregnant and lactating women. This dose corresponds to ~2730 mg L-threonate and 250 mg magnesium, which also corresponds to the UL for supplemental magnesium from readily dissociable magnesium salts. Based on results obtained from a dissociation study, two rat studies and one human trial, the Panel considers that magnesium is bioavailable from the NF. The NF may contain up to 1% oxalic acid. The Panel considers that an additional exposure to oxalic acid, that is up to 30 mg daily from the NF, is not to be of safety concern. The Panel concludes that the NF is not nutritionally disadvantageous. In 2008, the EFSA ANS Panel concluded that a human intake of L-threonate of 2700 mg per day is safe. This intake is similar to the maximum intake of L-threonate from the NF under the maximum proposed uses, and the NDA Panel concurs with the ANS Panel that this intake is safe. The Panel considers that there are no concerns regarding the genotoxicity of the NF. The Panel concludes that the NF, Mg L-threonate, is safe under the proposed conditions of use. The Panel concludes that the NF is a source from which magnesium is bioavailable.

KEYWORDS

bioavailability, food supplement, magnesium L-threonate, novel foods, nutrient source, safety

CONTENTS

1 | INTRODUCTION

1.1 | Background and Terms of Reference as provided by the requestor

The European Union legislation lists nutritional substances that may be used for nutritional purposes in certain categories of foods as sources of certain nutrients. The relevant Union legislative measures are:

- Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods.[1]
- Directive 2002/46/EC of the European Parliament and of the Council on food supplements.[2]

On 24 March 2021, the company AIDP Inc. submitted an application to the European Commission in accordance with Article 10 of Regulation (EU) 2015/2283 to authorise the placing on the Union market of magnesium (Mg) L-threonate as a novel food.

The applicant requests for Mg L-threonate to be used as a novel food in food supplements as defined in Directive 2002/46/EC, excluding food supplements for infants and young children.

The applicant has also requested data protection under Article 26 of Regulation (EU) 2015/2283.

The Commission is of the opinion that the novel food, Mg L-threonate, should be considered as a source of magnesium in the context of the relevant legislation.

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002, the European Commission asks EFSA to provide a scientific opinion:

– by carrying out the assessment of Mg L-threonate as a novel food in accordance with Article 10(3) of Regulation (EU) 2015/2283;
– following the outcome of the novel food assessment, by evaluating the safety and bioavailability of the novel food when added for nutritional purposes as a source of magnesium to food supplements, excluding food supplements for infants and young children.

The Commission also asks EFSA to evaluate and inform the Commission as to whether and if so, to what extent, the requirements of Article 26(2)(c) of Regulation (EU) 2015/2283 are fulfilled in elaborating its opinion on Mg L-threonate regarding the proprietary data for which the applicant is requesting data protection.

1.2 | Information on existing evaluations and authorisations

In 2001, the Scientific Committee on Food (SCF) determined an Upper Intake Level (UL) on the basis of human studies with adults and children in which mild diarrhoea occurred after ingestion of magnesium supplements and in which information on magnesium intake from foods and beverages was not available (SCF, 2001). A No Observed Adverse Effect Level (NOAEL) of 250 mg/day was derived from these human studies, and an uncertainty factor of 1 was applied to establish an UL of 250 mg/day for adults, including pregnant and lactating women, and children from 4 years of age and older. The SCF considered that the UL applies for readily dissociable magnesium salts (e.g. chloride, sulphate, aspartate and lactate) and compounds like magnesium oxide (MgO), in food supplements, water or added to food and beverages. This UL does not include magnesium, which is normally present in foods and beverages.

In 2015, the EFSA NDA Panel noted that average requirements and population reference intakes for magnesium cannot be established, but that adequate intakes (AIs) based on observed intakes in healthy populations in the EU could be established (EFSA NDA Panel, 2015). Accordingly, 300 and 350 mg/day per day have been considered as AIs for women (also if pregnant and lactating) and men, respectively. For children aged 10 to < 18 years, an AI for magnesium has been set at 300 mg/day for boys and 250 mg/day for girls. For children aged 3–< 10 years, an AI for magnesium has been set at 230 mg/day for both sexes.

In 2008, the EFSA ANS Panel (2008) assessed the safety of calcium (Ca) L-threonate and the bioavailability of calcium from this substance when used in food supplements. In their Opinion, the EFSA ANS Panel concluded that up to 4 tablets per day, each providing 100 mg calcium and 675 mg L-threonate, corresponding to a daily intake of 400 mg calcium and 2700 mg L-threonate, are not of safety concern.

Following that assessment by the EFSA ANS Panel, Ca L-threonate has been authorised for its use in food supplements in Europe under Regulation (EU) 1170/2009[3] amending the food supplement Directive 2002/46/EC.

[1]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. OJ L 327. 11.12.2015, p. 1.

[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, p. 51.

[3]https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32009R1170&from=RO

2 | DATA AND METHODOLOGIES

2.1 | Data

The safety assessment of this NF is based on data supplied in the application and information submitted by the applicant following an EFSA request for supplementary information.

Administrative and scientific requirements for NF applications referred to in Article 10 of Regulation (EU) 2015/2283 are listed in the Commission Implementing Regulation (EU) 2017/2469.[4]

A common and structured format on the presentation of NF applications is described in the EFSA guidance on the preparation and presentation of a NF application (EFSA NDA Panel, 2016). As indicated in this guidance, it is the duty of the applicant to provide all of the available (proprietary, confidential and published) scientific data (including both data in favour and not in favour) that are pertinent to the safety of the NF.

This NF application includes a request for protection of proprietary data in accordance with Article 26 of Regulation (EU) 2015/2283. The data requested by the applicant to be protected comprise a bioavailability study in rats, toxicological studies (in vitro bacterial reverse mutation assay, in vivo micronucleus test and a subchronic rat study) and a randomised, placebo-controlled human study.

2.2 | Methodologies

The assessment follows the methodology set out in the EFSA guidance on NF applications (EFSA NDA Panel, 2016) and the principles described in the relevant existing guidance documents from the EFSA Scientific Committee. The legal provisions for the assessment are laid down in Article 11 of Regulation (EU) 2015/2283 and in Article 7 of the Commission Implementing Regulation (EU) 2017/2469.

This assessment concerns only the risks that might be associated with the consumption of the NF under the proposed conditions of use, and is not an assessment of the efficacy of the NF with regard to any claimed benefit.

The evaluation of the bioavailability of the nutrient (magnesium) from the source (Mg L-threonate) was conducted in line with the principles contained in the 'Guidance on safety evaluation of sources of nutrients and bioavailability of nutrient from the sources' (EFSA ANS Panel, 2018).

3 | ASSESSMENT

3.1 | Introduction

The NF, which is the subject of the application, is composed of almost 100% pure Mg L-threonate monohydrate. The NF is produced from the raw materials ascorbic acid and calcium carbonate, followed by a substitution of calcium with magnesium. The NF falls under the category 'ix) Vitamins, minerals and other substances used in accordance with Directive 2002/46/EC, Regulation (EC) No 1925/2006 or Regulation (EU) No 609/2013'. The NF is intended to be used in food supplements. The target population is the general adult population, excluding pregnant and lactating women.

3.2 | Identity of the NF

The NF is an ingredient composed of almost 100% of Mg L-threonate monohydrate, as demonstrated by proximate analysis and elemental analysis. Mg L-threonate is an organic salt made of L-threonate anion and magnesium cation in a 2:1 ratio. A proton nuclear magnetic resonance (^{1}H-NMR) analysis was performed, and IR spectra were obtained, which proved its identity. According to the information provided by the applicant on the specific optical rotation of three batches of the NF and the information on the method, the results (+16.0°, +16.2° and + 17.0°) correspond to Mg L-threonate monohydrate.

The chemical identity and the chemical structure of the NF are presented in Table 1. To prove that the NF is an organic salt made of L-threonic acid anion and magnesium ion, the applicant refers to Fourier transform infrared spectroscopy (FT-IR) analysis, showing the stretching vibration of the carboxylate group of L-threonate at wavenumbers 1610 ~ 1550 cm^{-1} and 1450 ~ 1500 cm^{-1}, and lacking that corresponding to the protonated carboxyl group at 1725 ~ 1700 cm^{-1}. The identity of L-threonic acid in the NF has been demonstrated by high-performance liquid chromatography (HPLC) by comparison with an authentic specimen of L-threonic acid.

[4]Commission Implementing Regulation (EU) 2017/2469 of 20 December 2017 laying down administrative and scientific requirements for applications referred to in Article 10 of Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. OJ L 351, 30.12.2017, pp. 64–71.

TABLE 1 Chemical identity of the NF 'Mg L-threonate' as provided by the applicant.

Chemical substance	
Chemical (IUPAC) name	Magnesium (2R,3S)-2,3,4-trihydroxybutanoate monohydrate
Common name	Magnesium L-threonate
Other names: Synonyms, trade names, abbreviations	Magnesium L-threonate monohydrate, FDI-UNII code: 1Y26ZZ0OTM
Trade name	Magtein®
CAS number	500304–76-7
Molecular formula	$C_8H_{16}MgO_{11}$
Molecular weight	312.5 Da

Abbreviations: CAS, chemical abstracts service, IUPAC, International Union of Pure and Applied Chemistry.

3.3 | Production process

According to the information provided, the NF is produced in line with current Good Manufacturing Practice (GMP), Hazard Analysis Critical Control Points (HACCP) principles and a valid registration status at the FDA as a (US) domestic food facility. An HACCP plan for the manufacturing process of the NF has been provided.

The production process of the NF starts with the chemical synthesis of calcium L-threonate by means of the oxidation of ascorbic acid by H_2O_2 in the presence of calcium carbonate. Then calcium is substituted with magnesium through the addition of magnesium carbonate and oxalic acid. The further production steps comprise centrifugation (to remove water-insoluble calcium oxalate), neutralisation, decolouration with activated carbon, condensation, crystallisation with anhydrous ethanol, centrifugation and drying before packaging of the obtained powder. Certificates of analyses of the raw materials have been provided.

According to the applicant, the NF will be packaged in a 25 kg fibre drum or 25 kg corrugated carton, double bagged with polyethylene liners and stored in sealed containers, not exposed to excess heat and light.

According to a certificate, the applicant is registered and is listed as a manufacturer for human drugs pursuant to title 21, part 207 et. seq. of the US Code of Federal Regulations.

In response to an EFSA question on how the oxidation reaction is controlled to obtain pure L-threonic acid from ascorbic acid and H_2O_2, the applicant referred to an 1H-NMR analysis that did not indicate organic by-products and provided analytical information on oxalic acid content.

The Panel considers that the production process is sufficiently described.

3.4 | Compositional data

According to the application, the identity of Mg L-threonate in every batch is confirmed by FT-IR. The content of L-threonate is measured by HPLC, and magnesium is quantified by complexometric titration with ethylenediaminetetraacetic acid (EDTA) or ICP-MS. The FT-IR scans from three batches have been provided.

In order to confirm that the manufacturing process is reproducible and adequate to produce on a commercial scale a product that complies with the proposed specifications, the applicant provided analytical information from 12 independent batches of the NF (Table 2). One batch from 2010 and six from 2012 were tested for their magnesium and L-threonate contents, heavy metals and microbiological parameters. Testing of five more recent batches from 2019 also included information on physical characteristics such as bulk density, particle size and loss on drying. Certificates of analyses were provided for the six batches from 2019, but not for the batches produced in 2010 and 2012. The batch testing shows that the NF is composed of almost 100% Mg L-threonate monohydrate. The magnesium content ranged between 7.5% and 8.8%, and L-threonate ranged between 86.3% and 89.1%.

According to the certificates of analyses for three additional batches from 2020 (not presented in a Table in this opinion), the concentrations for magnesium ranged between 7.4% and 8.0%, and the range for L-threonate was 88.3%–91.4%.

The five batches from 2019 were tested for ethanol by gas chromatography (USP 467) and showed concentrations between 131 and148 ppm; no other solvents were used in the production process, according to the applicant (Table 2). One batch produced in 2011 and two in 2012, analysed by an external lab, had ethanol concentrations below 10 ppm (not presented in a Table in this opinion).

Following a request by EFSA regarding side products from the production process, the applicant provided analytical results on residual calcium (0.0062%–0.0149%) for three batches. One batch was analysed for oxalic acid content (0.155%), magnesium (7.80%) and threonic acid (89.3%). ^{1}H-NMR analysis of one batch did not reveal organic by-products of the chemical synthesis. The Panel notes that the range for oxalic acid of three other batches used for the stability testing (Table 3) was 0.2%–0.5%.

In addition to the analyses for heavy metals presented in Table 2, the applicant provided results on arsenic, mercury, lead and cadmium contaminations in an additional six batches (each three from 2020 and 2021). The values for these four heavy metals ranged between < 0.001–0.081 ppm, < 0.001–0.008, 0.003–0.02 and < 0.001–0.001 ppm, respectively.

TABLE 2 Batch to batch analysis of the NF.

Parameters	Method	2019–1	2019–2	2019–3	2019–4	2019–5	2010–1	2012–1	2012–2	2012–3	2012–4	2012–5	2012–6
Appearance	Visual	White powder	White powder	White powder	White powder	White powder	White powder	NA	NA	NA	NA	NA	NA
Odour and taste	Organoleptic	Conf.	Conf.	Conf.	Conf.	Conf.	NA	NA	NA	NA	NA	NA	NA
Solubility	Visual (1% at 25°C)	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	NA	NA	NA	NA	NA	NA
Colour of solution	Visual (1% solution)	Conf.	Conf.	Conf.	Conf.	Conf.	NA	NA	NA	NA	NA	NA	NA
Bulk density	Loose fill in graduated cylinder	0.68 g/mL	0.72 g/mL	0.77 g/mL	0.67 g/mL	0.68 g/mL	NA	NA	NA	NA	NA	NA	NA
Particle size NLT 90% thru a US # 20 (0.841 mm)	Ro Tap Sieve shaker (3 min)	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	NA
NMT 60% thru a US # 200 (0.074 mm)	Ro Tap (3 min)	25	31	30	30	32	NA	NA	NA	NA	NA	NA	NA
Identification	IR	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	NA	NA	NA	NA	NA	NA
Loss on drying (%)	105°C, 4 h	0.4	0.3	0.2	0.3	0.1	Conf.	NA	NA	NA	NA	NA	NA
Mg L-threonate monohydrate (%)	Titration	100.6	100.5	100.7	100.6	100.5	Conf.	NA	NA	NA	NA	NA	NA
Magnesium (%)	ICP-OES	7.7	7.7	7.7	7.7	7.7	7.6	7.6	7.5	7.7	7.7	7.8	7.8
L-threonate (%)	HPLC	NA	NA	NA	NA	NA	87.4	88.8	88.8	89.1	88.2	87.7	86.3
Ethanol (ppm)	USP 467 (GC)	136	138	148	147	131	NA	NA	NA	NA	NA	NA	NA
pH	USP (1% in H_2O)	6.3	6.4	6.4	6.4	6.4	NA	NA	NA	NA	NA	NA	NA
Arsenic (ppm)	ICP-MS	0.011	0.014	0.012	0.038	0.019	< 0.2	0.370	0.779	0.494	0.508	0.365	0.745
Mercury (ppm)	ICP-MS	0.002	0.007	0.006	0.001	0.033	< 0.05	< 0.001	0.021	0.004	0.002	< 0.001	< 0.001
Lead (ppm)	ICP-MS	0.042	0.044	0.030	0.036	0.028	< 0.05	0.057	0.208	0.087	0.151	0.069	0.083
Cadmium (ppm)	ICP-MS	0.005	0.004	0.008	0.003	< 0.001	< 0.05	0.001	0.001	0.002	0.005	0.002	0.003
Total plate count (cfu/g)	USP <2021>	10	10	10	< 10	10	< 3000	≤ 10	≤ 10	75	≤ 10	≤ 10	≤ 10
Yeast and mould (cfu/g)	USP <2021>	< 10	< 10	< 10	< 10	< 10	< 300	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10
E. coli	USP <2022>	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
Salmonella	USP <2022>	Neg	Neg	Neg	Neg	Neg	NA	Neg	Neg	Neg	Neg	Neg	Neg

Abbreviations: Cfu, colony forming unit; conf., conforms; GC, gas chromatography; ICP-OES, Inductively coupled plasma–optical emission spectrometry; ICP-MS, inductively coupled plasma mass spectrometry; IR, infrared; NA, not available; Neg, negative; NLT, not larger than; USP, United States Pharmacopeia.

Information was provided on the accreditation of the laboratories that conducted the analyses presented in the application.

The Panel considers that the information provided on the composition is sufficient to characterise the NF.

3.4.1 | Stability

The stability of the powder was investigated in three batches at 25°C ± 2°C and 60% RH ± 5% for 36 months (Table 3). The results of a stability study (not shown) under accelerated conditions (at 40°C and 75% RH) for 6 months were consistent with the data obtained under ambient conditions.

TABLE 3 Stability testing of the NF as a powder.

	Month 0			Month 36		
Parameter	**2015–1**	**2015–2**	**2015–3**	**2015–1**	**2015–2**	**2015–3**
pH value	6.9	6.3	6.4	6.9	6.3	6.4
Loss on drying	0.1%	0.1%	0.2%	0.1%	0.1%	0.2%
L-Threonate	88.7%	88.2%	86.5%	85.8%	86.6%	86.0%
Oxalic acid	0.4%	0.3%	0.2%	0.4%	0.3%	0.2%
Magnesium	7.6%	7.8%	7.8%	7.6%	7.6%	7.6%
Assay	99.6%	100.8%	100.9%	98.6%	98.6%	98.4%
Bacterial count	< 10 cfu/g	< 10 cfu/g	< 10 cfu/g	< 10 cfu/g	< 10 cfu/g	< 10 cfu/g
Yeast and mould	< 10 cfu/g	< 10 cfu/g	< 10 cfu/g	< 10 cfu/g	< 10 cfu/g	< 10 cfu/g
E. coli	ND	ND	ND	ND	ND	ND
Salmonella	ND	ND	ND	ND	ND	ND

Abbreviations: Cfu, colony forming unit; ND, not detected.

The Panel considers that the data provided sufficient information with respect to the stability of the NF.

3.5 | Specifications

The specifications of the NF are indicated in Table 4.

TABLE 4 Specifications of the NF as proposed by EFSA.

Parameter	Specification
Loss on drying	≤ 5.0%
Mg L-threonate monohydrate	98%–102%
Magnesium	7.2%–8.3%
L-Threonate	82%–91%
Oxalic acid	≤ 1%
Ethanol	≤ 5000 ppm
Microbiological	
TAMC	≤ 100 CFU/g
Yeast and mould	≤ 10 CFU/g
E. coli	ND/10 g
Salmonella	ND/25 g

Abbreviations: cfu, colony forming units; ND, not detected; TAMC, total aerobic microbial count.

The Panel considers that the information provided on the specifications of the NF is sufficient and does not raise safety concerns.

3.6 | History of use of the NF and/or of its source

3.6.1 | History of use of the NF

A generally recognized as safe (GRAS) dossier (GRN No 499, 2014) for the NF has been reviewed by the US FDA in 2014 for its use in food and food supplement as magnesium source. The FDA did not raise questions (FDA, 2014).

According to the applicant, Mg L-threonate is sold in USA since 2010. The NF is currently sold in USA and Canada as a dietary supplement at dose up to 4000 mg/day for adults. In 2020, over 100 tons of the NF were sold, according to the applicant. The applicant has not become aware of adverse events following the consumption of the NF.

3.7 | Proposed uses and use levels and anticipated intake

3.7.1 | Target population

The target population proposed by the applicant is the general adult population, excluding pregnant and lactating women.

3.7.2 | Proposed uses and use levels

The applicant intends to market the NF for use in food supplements, at a maximum dose of 3000 mg of the NF per day, which corresponds to ~250 mg magnesium and 2730 mg L-threonate per day.

3.8 | Absorption, distribution, metabolism and excretion (ADME)

3.8.1 | In vitro data

A dissociation study with the NF was conducted at pH 2 and 7 (Patel, 2020). The dissociation of magnesium L-threonate was measured by HPLC-UV (L-threonic acid) and ICP-MS (magnesium), and the identification of the starting material as Mg L-threonate by HPLC-MS. The results of the HPLC-UV analysis showed that the solution of Mg L-threonate gave a clear peak at 2.45 min for L-threonic acid at pH 2, whereas no peak was found at the neutral pH. Similarly, the results of the ICP-MS analysis showed the presence of dissociated magnesium ion in the Mg L-threonate solution at pH 2. Moreover, the HPLC-MS revealed that for the aqueous solution of Mg L-threonate at neutral pH in positive mode electrospray conditions, molecular ion $[M+2H]^+$ at m/z 296.67 was observed, representing magnesium L-threonate, whereas at pH 2 in negative mode, molecular ion $[M\text{-}H]^-$ at m/z 135.04 was observed, representing the threonate moiety.

Altogether, the results obtained from this in vitro dissociation study indicate the dissociation of Mg L-threonate at pH 2. The applicant considers that this study suggests that after oral administration of magnesium L-threonate, magnesium and L-threonate would dissociate in the gastrointestinal tract at gastric pH (between 1 and 3). When considering that the acid dissociation constant (pKa) of L-threonic acid is about 3.5, it can be calculated that the dissociation at pH 3.5 is about 50%. At pH 2.5 and lower pH, the dissociation would be about 90% and higher, respectively.

3.8.2 | Animal data

In a study with adult male Sprague Dawley rats, the absorption, excretion and retention of magnesium from the NF were compared with those from magnesium chloride, magnesium gluconate and magnesium citrate (Zhao et al., no date, unpublished). The animals (8–10 per group) were kept individually in metabolic cages for 12 days and received, from Days 4 to 10, one of these four magnesium compounds. Concentrations that corresponded to either 0.33 or 1 mg/mL of elemental magnesium in the drinking water were used. Drinking water could be consumed ad libitum. On the basis of the measured water consumption, the daily magnesium intake was calculated for each rat. The diet of the rats was magnesium-deficient (29.4 μg/g feed) to neglect magnesium intake with the feed.

From Days 11 to 12, rats received de-ionised water (without added magnesium). The urine, from each rat, was collected on a daily basis during the magnesium supplementation period (Days 4–10), while faecal pellets were collected from Days 5 to 11. The collected urine and faecal pellets from each rat from all days were then pooled, and the total volume of the pooled urine and total weight of faeces for each individual rat were recorded. The pooled urine and faecal pellets from each individual rat were analysed for magnesium content using ICP-AES, and the total magnesium content in urine and faeces was determined.

For each individual rat, absorption was calculated and expressed as the relative amount (%) of the difference between Mg^{2+} intake and faecal Mg^{2+} excretion compared to the Mg^{2+} intake (×100).

Relative urinary Mg^{2+} excretion was expressed as the % of the urinary Mg^{2+} excretion of the absorbed amount of Mg^{2+}.

Relative retention was expressed as the % of the absorbed Mg^{2+} minus Mg^{2+} excreted with the urine compared to the Mg^{2+} intake (×100).

The results for all individual rats on these three endpoints (relative absorption, relative urinary excretion and relative retention) were plotted, and linear regression analysis was performed for each group of rats receiving one of the four magnesium components to determine the slope for each of them. The manuscript provided only the slopes for Mg L-threonate and magnesium chloride. The relative absorption of magnesium from Mg L-threonate (about 60%) was reported to be statistically significantly higher as compared to the relative absorption from magnesium chloride, magnesium gluconate and magnesium citrate (which was about 40%–45%). No statistically significant difference was reported for the relative urinary Mg^{2+} excretion. The retention was reported to be statistically significantly higher for the group of rats receiving Mg L-threonate.

Slutsky et al. (2010) studied the effect of Mg L-threonate intake on the Mg^{2+} concentration of the cerebrospinal fluid (CSF).

Mg L-threonate was added to drinking water at concentrations targeting a dose of 50 mg/kg bw per day elemental magnesium, which corresponds to ~604 mg Mg L-threonate per kg bw per day. The Mg^{2+} concentration in the CSF was measured at baseline, Day 12 and Day 24. A control group without Mg^{2+} supplementation was used to evaluate the loss of Mg^{2+} associated with the CSF sampling. The feed contained 0.15% elemental magnesium.

The authors reported an increase in CSF Mg^{2+} concentration at Days 12 and 24 compared to baseline and the control group. At Day 24, this increase was statistically significant by about 7% and 16% as compared to baseline and the control group, respectively. The loss of Mg^{2+} in the control group was attributed by the authors to the sampling of CSF (on Days 0 and 12).

The Panel considers that the two studies provided by the applicant (Slutsky et al., 2010; Zhao et al., no date, unpublished) indicate that magnesium from Mg L-threonate is bioavailable in rats.

3.8.3 | Human data

A human study (Liu et al., 2016; Krieger, 2013; unpublished study report) with the NF provided by the applicant included endpoints related to the magnesium status and suggested that magnesium was bioavailable from the NF (described in Section 3.10.5 Human data).

In a single- and multiple-dose study, 12 generally healthy adult men between 19 and 40 years of age were randomly assigned to receive either a single dose of 675, 2025 or 4050 mg Ca L-threonate after overnight fasting or a single dose of 2025 mg taken within 30 min after breakfast (Wang et al., 2011). Another 12 volunteers (with the same characteristics) received 2025 mg twice per day for 4 days. Plasma and urine L-threonate concentrations were measured by HPLC–MS/MS. The mean plasma half-life ($t_{1/2}$) for all single-dose groups was about 2.5 h. While the mean plasma t_{max} in all single-dose groups with fasted subjects was 2 h, those who received Ca L-threonate shortly after breakfast had a t_{max} of about 3 h. The latter group, which received 2025 mg Ca L-threonate within 30 min after breakfast, had a higher area under the curve ($AUC_{0\text{-}t}$) and C_{max}, which were about 33% and 21% higher than the group that received 2025 mg Ca L-threonate given after overnight fasting. These two parameters (AUC and C_{max}) increased, although disproportionally lower than the dose (among the fasted groups). A linear dose proportionality was not observed. The cumulative urinary excretion of L-threonate over 24 h represented only 10.3, 4.2 and 3.3% of the three single-dose groups with a mean renal clearance of 0.8 L/h. No accumulation was observed after repeated doses of 2025 mg twice daily for 4 days. Only one minor adverse event (mild, transient diarrhoea) was reported in this study in a subject who received a single dose of 2025 mg calcium L-threonate. In order to investigate whether L-threonate could have been eliminated as a conjugated form, the authors analysed the urine samples using high-resolution mass spectrometry, which did not find phase II metabolites.

EFSA has noted in several opinions that threonic acid arises from the catabolism of ascorbic acid by oxidation, along with other oxidation products such as oxalic acid, xylose, xylonic acid and lyxonic acid (EFSA, 2004; EFSA AFC Panel, 2007; EFSA ANS Panel, 2015; EFSA NDA Panel 2013). Considering the limited and saturating absorption of vitamin C at daily intakes above 1 g and the increasing urinary excretion at daily intakes above 100 mg (EFSA, 2004; EFSA NDA Panel, 2013), the Panel considers that an intake of 2730 mg L-threonate per day at the proposed maximum intake of the NF, would result in a higher systemic exposure to L-threonate as compared to L-threonate arising from vitamin C metabolism. The Panel notes that the available information on the metabolic fate of threonic acid in the human body is very limited, and the conversion of threonic acid to oxalic acid has not been reported. In the study by Wang et al. (2011), no accumulation of L-threonate in the plasma was observed after repeated doses of 2025 mg twice daily for 4 days.

Considering the provided in vitro dissociating study, the two rat studies and the data provided in humans, the Panel considers that magnesium from the NF is bioavailable.

3.9 | Nutritional information

The Panel notes that the proposed maximum intake of magnesium from the NF corresponds to ~250 mg magnesium per day, which is below the AI (i.e. 300 mg/day for women and 350 mg/day for men) established for magnesium by the EFSA NDA Panel (2015). However, 250 mg per day is the UL for supplemental magnesium from readily dissociable magnesium salts on top of the magnesium intake from the background diet established by the SCF (2001).

Batch testing provided by the applicant showed oxalic acid concentrations up to 0.5% in the NF. Considering the proposed specification limit (i.e. ≤ 1%) and the maximum proposed use level of 3000 mg/per day, the resulting intake of oxalic acid from this NF could be up to 30 mg per day. Such exposure appears to be small when considering the natural occurrence of oxalic acid reported for some vegetables, fruits and other foods (in FW), for example 400–900 mg/100 g spinach, 275–1336/100 g rhubarb, 230 mg/100 g cashew, 20–141 g/100 g potatoes and up to 30 mg per 100 g in apples and tomatoes (Noonan & Savage, 1999).

The Panel considers that additional exposure to oxalic acid, that is up to 30 mg per day, from the NF would not be of concern in terms of calcium binding or potential toxicity for the target population, that is the general adult population.

The Panel considers that the consumption of NF at the proposed conditions of use is not nutritionally disadvantageous.

3.10 | Toxicological information

Initially, the applicant had provided a bacterial reverse mutation test, an in vivo mammalian micronucleus (MN) test, an acute oral toxicity LD_{50} study and a subchronic toxicity study in rats, all claimed by the study reports to be compliant with respective Organisation for Economic Co-operation and Development (OECD) Guidance documents and Good Laboratory Practice (GLP). In addition, the applicant also provided a tolerability study in rats with the aim to determine and to compare the dose of Mg L-threonate with three other magnesium compounds, which cause diarrhoea in 50% (TD_{50}) of the rats.

In line with the requirements set in the EFSA Novel Food Guidance (EFSA NDA Panel, 2016) and the Guidance of the EFSA Scientific Committee (2011) on genotoxicity testing strategies applicable to food and feed safety, EFSA requested an in vitro MN study in order to have a completed tier-1 (i.e. in vitro) genotoxicity testing battery. The Panel notes that performing a tier-2 in vivo mammalian MN test in mice in the absence of an inconclusive or positive result coming from completed tier-1 in vitro studies is neither in compliance with these two EFSA Guidance documents nor with the NF Regulation (EU) 2015/2283, which emphasises the 3 R's (replacing, reducing and refining animal studies). Similarly, the requirements set by the EFSA Novel Food Guidance (EFSA NDA Panel, 2016) do not include an acute toxicity study.

In response, the applicant provided an in vitro MN study (Kadam, 2022, unpublished). This study and the subchronic toxicity study (Saravanan, 2020, unpublished), both performed in the same test facility, raised EFSA's concerns regarding their GLP compliance. After consultation with and recommendation from the EFSA Working Group (WG) on GLP at their 7th WG meeting (EFSA WG GLP, 2023), EFSA requested a study audit of these two studies. The study audit report of the national competent authority noted for both concerned studies, several observations of severe nature, for which these studies cannot be considered as GLP studies.

The Panel notes that in order to ensure that toxicological studies are performed to a certain standard, the Commission Implementing Regulation (EU) 2017/2469 requires that toxicological studies are conducted in facilities that comply with the requirements of the Directive 2004/10/EC—or, if they are carried out outside the territory of the Union, they shall follow the OECD Principles of GLP. Hence, EFSA asked the applicant to provide a new GLP-compliant in vitro MN study. With regards to subchronic toxicity, the Panel considered (i) the purity of the NF, (ii) the production process, which does not raise safety concerns and (iii) that the safety of both of the moieties of Mg L-threonate, that is magnesium and L-threonate, at the proposed maximum daily intake of the NF has been already established (EFSA ANS Panel, 2008; SCF, 2001). Hence, the applicant was not requested to perform a new subchronic toxicity study. The two audited, non-GLP-compliant studies (Kadam, 2022, unpublished; Saravan, 2020, unpublished) are included in Table 5, but are not described in the following sections.

TABLE 5 List of toxicological studies with the NF.

Reference	Type of study	Test system	Max dose
Harke (2020), unpublished	Bacterial reverse mutation test OECD TG 471 (OECD, 2020), GLP	*S.* Typhimurium TA98, TA100, TA102, TA1535 and TA1537	Up to 5000 µg/plate (absence and presence of S9 mix)
Kadam (2022), unpublished	In vitro micronucleus test OECD TG 487 (OECD, 2016a) not in compliance with GLP	CHO-k1 cells	2000 µg NF/mL
Kadam (2023), unpublished	In vitro micronucleus test OECD TG 487 (OECD, 2023), GLP	CHO-k1 cells	2000 µg NF/mL
Kumar (2020), unpublished	In vivo mammalian erythrocyte micronucleus test OECD TG 474 (OECD, 2016b), GLP	Swiss Albino Mice	2000 mg NF/kg bw per day (oral gavage)
Saravanan (2020), unpublished	90-day subchronic toxicity study OECD TG 408 (OECD, 2018) not in compliance with GLP	Sprague Dawley rats	2000 mg NF/kg bw per day
Zhao et al. (no date), unpublished	Gastrointestinal tolerability	Sprague Dawley, adult male rats	150 mg[a]/kg bw per day

Abbreviations: CHO, Chinese hamster ovary; GLP, Good Laboratory Practice; NF, novel food; OECD TG, Organisation for Economic Co-operation and Development for testing of chemicals.

[a]Elemental magnesium from Mg L-threonate (corresponding to ~ 1800 mg/kg bw per day).

3.10.1 | Genotoxicity

In the in vitro bacterial reverse mutation assay, Salmonella Typhimurium strains TA98, TA100, TA102, TA1535 and TA1537 were treated with the NF (Harke, 2020, unpublished). In this study, the test item was non-mutagenic at concentrations up to 5000 μg/plate in the absence or presence of (S9) metabolic activation.

Upon an EFSA request, the applicant conducted a second, new in vitro mammalian cell MN test using CHO-k1 cells following OECD TG 487 and in compliance with GLP principles (Kadam, 2023, unpublished). Since neither precipitation nor cytotoxicity were found at concentrations of 31.25, 62.5, 125, 250, 500, 1000 and 2000 μg of the NF/mL, concentrations of 500, 1000 and 2000 μg/mL were used for the main study, which included an untreated control, a vehicle control (MilliQ water) and positive controls (treated with cyclophosphamide monohydrate, mitomycin-C and vinblastine) in the presence and absence of S9 metabolic activation. There was no increase in MN-binucleated cells as compared to the untreated and vehicle controls.

In an in vivo mammalian micronucleus study with Swiss Albino mice, the test item did not induce MN in the immature (polychromatic) erythrocytes at doses of 500, 1000 and 2000 mg of the NF/kg bw given per oral gavage for two consecutive days (Kumar, 2020, unpublished).

Taking into account the test results provided and considering the composition and production process of the NF, the Panel considers that there are no concerns regarding genotoxicity.

In 2008, the ANS Panel came to the same conclusions in their assessment of Ca L-threonate.

3.10.2 | Subchronic toxicity

As noted above, the 90-day rat study could not be used to evaluate the subchronic toxicity of the NF. However, the safety of moiety L-threonate has been already established by EFSA. The assessment of the EFSA ANS Panel (2008) on the safety and bioavailability of calcium (Ca) L-threonate included two subchronic toxicity studies, one performed in rats receiving 0, 2, 4 or 6 g/kg bw per day, and the other one in dogs, which received 0, 1, 2 or 3 g/kg bw per day.

Adverse effects were found in both of these studies. In the rat study, the highest dose (6 g/kg bw per day) group males showed a statistically significant shorter blood coagulation time and a mild thyroid gland accretion. Both effects were reversible and not seen in the high-dose female rats. In the dog study, a reversible slight hyperplasia of the thyroid gland was reported in the medium (2 g/kg bw per day) and high dose (3 g/kg bw per day) groups. The ANS Panel concluded that the NOAELs of these studies are 4 g/kg bw per day for the rat study and 1 g/kg bw per day for the dog study, respectively. The reported adverse effects at higher dose were attributed by the ANS Panel to the high calcium intake.

With regards to the L-threonate moiety, the NOAELs correspond to 3484 mg/kg per day in the rat study and 871 mg/kg per day in the dog study. The margins of exposure to the maximum daily intake of L-threonate by human were considered sufficient by the ANS Panel, who noted that L-threonate is an endogenous compound in the body and that the adverse effects observed in the two subchronic studies were not attributable to L-threonate but to calcium.

3.10.3 | Reproductive and developmental toxicity

No reproductive and developmental toxicity studies have been provided on the NF.

In their Opinion on Ca L-threonate, the EFSA ANS Panel (2008) noted that the results from the provided studies in mice indicated that Ca L-threonate had no adverse effect on fertility and the developing fetus up to the highest dose tested (6 g/kg bw per day). Such dose corresponds to ~ 5.2 g L-threonate/kg bw per day.

3.10.4 | Other animal studies

In another experiment described in the study report by Zhao et al. (no date), unpublished), which is described in the ADME section, the dose required to induce diarrhoea in 50% of the adult rats was determined. The same magnesium compounds used to study absorption, faecal and urinary excretion and retention (i.e. the NF, magnesium chloride, magnesium gluconate and magnesium citrate) were used. The compounds were dissolved in deionised water at concentrations aiming to achieve daily magnesium intakes via the drinking water of 15, 50, 90 and 150 mg/kg bw and were given to rats (10 per group, kept in individual cages) for 4 days. The laxative effects were measured by the number of animals that get diarrhoea (defined as 'frequent watery feces that were closer to droppings than to dried pellets'). The average actual intakes for each of the four dose groups and for each of the four magnesium components were then plotted against the % of the animals experiencing diarrhoea, and the data were analysed using non-linear fit with variable Hill slope in order to determine the dose that causes diarrhoea in 50% of the rats. These doses were 89.9, 99.7 and 131.5 mg Mg^{2+}/kg bw for magnesium chloride, magnesium gluconate and Mg L-threonate, respectively. The dose of 131 mg Mg^{2+}/kg bw corresponds to 1589 mg/kg bw Mg L-threonate. Those rats that had received magnesium citrate stopped water consumption at a dose of 90 mg/kg bw per day. At that intake level, 3 out of 10 rats had developed diarrhoea. At a dose of 50 mg Mg^{2+}/kg bw provided by Mg L-threonate, no rat had diarrhoea.

3.10.5 | Human data

Three human studies were provided by the applicant: one randomised, double-blind, placebo-controlled trial (Liu et al., 2016; Krieger, 2013, unpublished study report) that studied the NF, and two open-label studies with Mg L-threonate anhydrous ($C_8H_{14}MgO_{10}$) (Surman et al., 2021; Wroolie et al., 2017). In addition to these three studies provided by the applicant, EFSA retrieved an additional randomised, double-blind, placebo-controlled trial (Zhang et al., 2022).

A randomised, double-blind, placebo-controlled trial performed in Miami (US) enrolled 51 adults (36 women, 15 men), aged–70 years, who received a daily dose of 1.5 or 2 g/day to study the effects of a 12-weeks' dietary supplementation with the NF (Liu et al., 2016; Krieger, 2013, unpublished study report).

The subjects had self-reported complaints of cognition (memory and concentration) but were otherwise generally healthy. Two other inclusion criteria were sleep disorder and anxiety. Eighteen women and seven men received the NF; 18 women and eight men received rice protein serving as placebo. Subjects of the NF group weighing between 50 and 70 kg bw received a daily dose of 1.5 g of the supplement (providing about 124 mg magnesium), and subjects between 70 and 100 kg bw received 2 g (providing 166 mg magnesium).

The trial aimed to study efficacy endpoints related to anxiety, mood, quality of sleep and cognitive function, but also included endpoints related to safety such as haematological parameters (white band red blood cell counts, haematocrit, haemoglobin, MCV, MCH, MCHC, platelet counts and mean volume), metabolic parameters (serum levels of sodium, potassium, calcium, chloride, carbon dioxide, blood glucose, blood urea nitrogen, creatinine, total protein, albumin, globulins, alkaline phosphatase, ALT, AST, GGT, bilirubin and uric acid), body weight, vital signs (heart rate, systolic and diastolic blood pressures) and adverse events. In addition, effects on parameters related to magnesium (plasma Mg, RBC Mg and urinary Mg) were studied.

The safety population consists of all subjects who received at least one dose of the NF or placebo. Study visits took place at screening and randomisation (visits 1 and 2), in the mid of the study at Week 6 (visit 3), and at the end of the study at Week 12 (visit 4).

There were no statistically significant changes observed regarding body weight, systolic and diastolic blood pressure or heart rate at any of the four visits. According to the study report, there were *'no clinically significant changes in safety laboratory results'*. In total, 47 adverse events (AEs) were reported for 28 out of 51 subjects in the safety population. The number of subjects experiencing AEs was similarly distributed between the NF group (13 subjects) and the placebo group (15 subjects), although the number of AEs was overall higher in the placebo group (30) compared to the NF group (17). The predominant adverse events were related to gastrointestinal function (5/25 subjects [20%] in the NF group vs. 4/26 [15.4%] subjects in the placebo group, $p = 0.726$) or infections/infestations (4/25 [16%] subjects of the NF group vs. 6/26 subjects [23.1%] in the placebo group, $p = 0.726$). Of the 47, 13 AEs were judged by the principal investigator to be 'possibly related' or 'probably related' to the intervention. Four of them were reported for four subjects in the dosed group, and nine were reported for four subjects in the placebo group. All 47 AEs in this trial were qualified as 'mild'. Those four AEs classified as probably or possibly related to the NF were loose stools, dry mouth, stomach upset and hypertension.

In an annex to the study report, the applicant presented the results on the endpoints related to magnesium. These endpoints comprised plasma Mg^{2+}, red blood cell Mg^{2+} and urinary Mg^{2+} normalised by the estimated glomerular filtration rate. All three parameters were increased at Weeks 6 and 12 in the group receiving the NF as compared to the baseline values. At Week 12, the urinary Mg^{2+} concentration in the NF group (+41%) was statistically significantly increased ($p = 0.048$) as compared to the placebo control (+8%). There was also a statistically significant increase ($p = 0.026$) in the NF group (+ 4.9%) for the plasma Mg^{2+} concentration at Week 6 as compared to the placebo group (−0.1%). The increase (+3.2%) observed at week 12 was statistically not significant ($p = 0.81$) compared to the placebo group (+2.5%). The increase of red blood cell Mg^{2+} in the NF group was statistically not significant compared to the placebo group, neither at Week 6 (+0.3% versus +4.1%, respectively) nor at Week 12 (+2.8% vs. −0.8%).

The Panel notes that the data provided on this RCT do not raise safety concerns. However, the Panel also notes the low number of subjects, the dose, which was only 2 g as compared to the proposed maximum dose of 3 g for the NF and the limited safety endpoints studied. The study suggests that magnesium is absorbed, as indicated by the increased urinary magnesium concentration.

In another randomised, double-blind, placebo-controlled trial conducted in China, 109 adult, healthy volunteers with a mean age of 60 (18–65) years received a daily dose of either 2 g of the NF or capsules with starch as a control for 30 days (Zhang et al., 2022). The main objective was to assess the potential beneficial effects of the NF on the cognitive function. Safety-related endpoints of this study included mental condition, sleep, heart rate and blood pressure; blood tests included white blood cells, red blood cells, haemoglobin and platelets; biochemistry parameters included serum total protein, albumin, alanine aminotransferase, aspartate aminotransferase, urea, creatinine, cholesterol, triglycerides and blood glucose. No statistically significant difference was found in any of the safety parameters, neither at baseline nor at the end of the study. The article did not report about the occurrence of adverse events. The drop-out rate for the NF group was 3/54 versus 4/55 in the placebo group.

In one 8-week open-label trial with a supplementation containing 1.8 g/day Mg L-threonate anyhydrous plus vitamin C and vitamin D in 15 patients over 60 years of age with mild to moderate dementia (Wroolie et al., 2017), no significant changes were observed in vital signs (heart rate, systolic and diastolic blood pressures, pulse) and body weight between baseline and study end (Wroolie et al., 2017). In another open-label trial, 15 patients of an average age of 36.4 ± 14.0 years

with attention-deficit/hyperactivity disorder were given 1.5–2 g/day of an anhydrous form of Mg L-threonate for 12 weeks (Surman et al., 2021). The authors of this study reported that no serious adverse events were observed in these trials.

Regarding the two open-label studies, the Panel notes some limitations of these studies for their use in this safety assessment, that is the open-label study design, the low number of subjects, the limited safety endpoints studied and the studied test material (i.e. Mg L-threonate anhydrous). The Panel therefore considers that these two studies do not provide evidence regarding the safety of the NF.

3.11 | Allergenicity

The Panel considers that the NF is unlikely to be allergenic as no protein-containing raw materials or reagents are used in the manufacturing process.

4 | DISCUSSION

The NF, which is the subject of the application, is Mg L-threonate, to be used as new source for magnesium in food supplements at a maximum dose of 3000 mg per day by adults, excluding pregnant and lactating women. This dose is equivalent to ~250 mg magnesium (corresponding to the UL for supplemental, readily dissociable magnesium) and 2730 mg L-threonate per day. The NF is produced by chemical synthesis. The NF is an ingredient composed of almost 100% of Mg L-threonate monohydrate, as demonstrated by proximate analysis and elemental analysis. The Panel considers that the production process is sufficiently described, that the information provided on the composition is sufficient for characterising the NF, and that the specifications do not raise safety concerns.

An in vitro dissociation study shows that Mg L-threonate is highly dissociated at a pH value of 2. Two rat studies indicate that magnesium is bioavailable from the NF. One randomised, double-blind, placebo-controlled human trial with 51 adults included parameters related to magnesium. Based on the results obtained by these studies, the Panel considers that magnesium is bioavailable from the NF.

The intake of magnesium, at the maximum intake of the NF as proposed by the applicant, is 250 mg per day, which corresponds to the UL for supplemental magnesium on top of the magnesium intake from the background diet established by the Scientific Committee on Food (2001). The NF may contain up to 1% oxalic acid. The Panel considers that an additional exposure to oxalic acid, that is up to 30 mg daily from the NF, is not to be of concern in terms of calcium binding or potential toxicity for the general adult population. The Panel concludes that the NF is not nutritionally disadvantageous.

Noting (i) the purity of the NF, (ii) the production process, which does not raise safety concerns and (iii) that the safety of both of the moieties of Mg L-threonate, that is magnesium and L-threonate, at the proposed maximum daily intake of the NF has been already established by EFSA (EFSA ANS Panel, 2008; SCF, 2001), the Panel considers that a subchronic toxicity study with the NF is not necessary to establish its safety. In 2008, the EFSA ANS Panel (2008) assessed the safety of calcium (Ca) L-threonate at a maximum proposed intake of 3100 mg per day, corresponding to about 2700 mg L-threonate daily. This is similar to the intake of L-threonate at the maximum daily intake (2730 mg per day) as proposed by the applicant for the NF in the present assessment. In the assessment of the EFSA ANS Panel, two subchronic toxicity studies were assessed. The margins of exposure between the NOAELs of these two studies and the maximum daily human intake of L-threonate at the proposed maximum proposed use levels (i.e. 2700 mg per day) were considered sufficient by the ANS Panel, who noted that L-threonate is an endogenous compound in the body and that the adverse effects observed in the two subchronic studies were not due to L-threonate but to the calcium doses. The NDA Panel agrees with the conclusions of the ANS Panel and considers these margins to be sufficient.

The Panel considers that there are no concerns regarding the genotoxicity of the NF.

5 | CONCLUSIONS

The Panel concludes that the NF, Mg L-threonate, is safe under the proposed conditions of use. The Panel concludes that the NF is a source from which magnesium is bioavailable.

5.1 | Protection of proprietary data in accordance with article 26 of regulation (EU) 2015/2283

Panel could not have reached the conclusion on the safety of the NF under the proposed conditions of use without the data claimed as proprietary by the applicant (a bioavailability study in rats, an in vitro bacterial reverse mutation assay and an in vivo micronucleus test) and the randomised, placebo-controlled human study.

6 | STEPS TAKEN BY EFSA

1. On 22/07/2021, EFSA received a letter from the European Commission with the request for a scientific opinion on the safety of magnesium L-threonate and to address the bioavailability of magnesium from this source in the context of Directive 2002/46/EC. Ref. letter 25072343.
2. On 22/07/2021, a valid application on magnesium L-threonate, which was submitted by the company AIDP Inc., was made available to EFSA by the European Commission through the Commission e-submission portal (NF 2021/2453), and the scientific evaluation procedure was initiated.
3. On 27/01/2022, 10/10/2022 and 28/02/2023 EFSA requested that the applicant provide additional information to accompany the application, and the scientific evaluation was suspended.
4. On 25/07/2022, 09/02/2023 and 27/11/2023, additional information was provided by the applicant through the Commission e-submission portal, and the scientific evaluation was restarted.
5. During its meeting on 30/01/2023, the NDA Panel, having evaluated the data, adopted a scientific opinion on the safety of magnesium L-threonate as a NF pursuant to Regulation (EU) 2015/2283 and the bioavailability of magnesium from this source in the context of Directive 2002/46/EC.

ABBREVIATIONS

^{1}H-NMR	proton nuclear magnetic resonance
ADME	absorption, distribution, metabolism and excretion
AFC	EFSA Panel on Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food
AI(s)	adequate intake(s)
ANS	EFSA Panel on Food Additives and Nutrient Sources added to Food
AUC	area under the curve
bw	body weight
CAS	Chemical Abstracts Service
CFU	colony forming unit
CHO	Chinese hamster ovary
c_{max}	maximum (plasma) concentration
CSF	cerebrospinal fluid
Da	Dalton
EDTA	ethylenediaminetetraacetic acid
FDA	(US) Food and Drug Administration
FDI-UNII	Foreign Drug Ingredient – Unique Ingredient Identifier
FT-IR	Fourier transform infrared spectroscopy
GC	gas chromatography
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GRAS	generally recognized as safe
GRN	GRAS notice
HACCP	Hazard Analysis Critical Control Points
HPLC	high-performance liquid chromatography
ICP-MS	inductively coupled plasma mass spectrometry
ICP-OES	inductively coupled plasma–optical emission spectrometry
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
LC–MS	liquid chromatography–mass spectrometry
LC–MS/MS	liquid chromatography with tandem mass spectrometry
MgO	magnesium oxide
MN	micronucleus
MS	mass spectrometry
NA	not available
NDA	Scientific Panel on Dietetic Products, Nutrition and Allergies
Neg	negative
NLT	not larger than
NOAEL	No Observed Adverse Effect Level
NF	novel food
OECD	Organisation for Economic Co-operation and Development
ppm	parts per million
RH	relative humidity
SCF	Scientific Committee on Food
t_{max}	time to maximum (plasma) concentration

UL	Tolerable Upper Intake Level
US	United States
USP	United States Pharmacopeia
UV	ultraviolet
WG	working group

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

QUESTION NUMBER

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