Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and materials in Contact with Food on a request from the Commission related to

Magnesium Aspartate as a mineral substance when used as a source of magnesium in dietary foods for special medical purposes.

Question number EFSA-Q-2004-066

Adopted on 7 January 2005

SUMMARY

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) has been asked to advice on the safety and bioavailability of the substance magnesium-L-aspartate when used as a source of magnesium in dietary foods for special medical purposes.
The Panel concluded that magnesium L-aspartate showed similar bioavailability to other organic magnesium salts and the more soluble inorganic magnesium salts. The Panel concluded that the use of magnesium-L-aspartate as a source of magnesium in dietary foods for special medical purposes is not of safety concern at the proposed levels of usage. The Panel concluded that there would be no safety concern from asparatate at the proposed usage levels.

KEYWORDS

magnesium-L-aspartate, foods for special medical purposes (FSMP)

BACKGROUND

This is an application for inclusion of magnesium-L-aspartate in Category 2 of the Annex to the Directive 2001/15/EC as a mineral (magnesium) substance which may be added to dietary foods for special medical purposes (FSMP). This substance is not currently included in the category of minerals in the Annex to Directive 2001/15/EC but magnesium-L-aspartate (magnesium salt of L-aspartic acid) is already included within the category of amino acids in the same Directive, and there are other sources of magnesium permitted in the mineral list. Prior to its inclusion in the amino acid category the safety of the substance as a whole should have been assessed.

Magnesium-L-aspartate is the magnesium salt of aspartic acid and like other magnesium salts of organic acids, is highly water soluble and readily absorbed in the intestine. Magnesium-L-aspartate has been used for many years both as a magnesium supplement for the maintenance of normal magnesium levels and as a licensed treatment (in Ireland, Germany, Switzerland and Austria) for hypomagnesaemia. The petitioner proposes to market granular magnesium-L-aspartate as a FSMP for the dietary management of magnesium deficiency.

The SCF established a tolerable upper intake level of 250 mg magnesium per day for readily dissociable magnesium salts (SCF 2001).

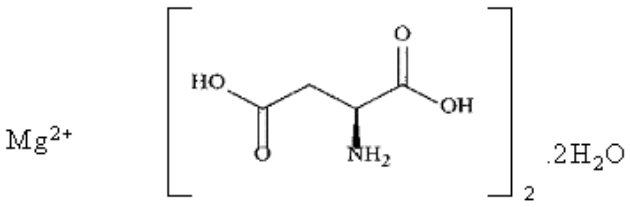
TERMS OF REFERENCE

The Commission asks EFSA to provide a scientific opinion, based on its consideration of the safety and bioavailability of the substance magnesium-L-aspartate when used as a source of magnesium in dietary foods for special medical purposes.

ASSESSMENT

Chemistry

Chemical name(s): Magnesium di[(S)-2-aminohydrogeno-butane-1,4-dioate]
Magnesium-L-Aspartate Dihydrate
CAS Number: 2068-80-6
Description
Physical form: Crystalline white powder
Structural formula



Molecular formula: $C_8H_{12}O_8N_2Mg*2H_2O$
Relative molecular mass: 324.5

Specifications

The material complies with the specification in the European Drug Master File (EDMF).

Manufacturing process

Details of the manufacturing process were provided as information in confidence to EFSA.

Existing authorisations and evaluations

Magnesium-L-aspartate has been marketed as a licensed medicinal product in European countries including Ireland, Switzerland, Austria and Germany. Magnesium-L-aspartate is already included in a variety of marketed food supplements (multivitamin/ mineral supplements) as a source of both magnesium and aspartic acid.

The sodium, potassium, calcium and magnesium salts of L-aspartic acid are included on the positive list (Annex) in Directive 2001/15/EC as acceptable sources of L-aspartic acid for use in foods for special medical purposes.

Case of need and proposed uses

According to the petitioner magnesium-L-aspartate has been used as a magnesium supplement for the maintenance of normal magnesium levels for many years as well as being a licensed treatment for hypomagnesaemia.

Exposure

The recommended adult daily intake proposed by the petitioner would contain magnesium-L-aspartate.$2H_20$ equivalent to about 240 mg of magnesium and 2600 mg of L-aspartic acid. The petitioner's recommended intake for children between 2-10 years is a half of this amount. The Recommended Dietary Allowance (RDA) of magnesium for normal adults is ~300 mg. Therefore the petitioner's recommended daily intake for adults of 240 mg of magnesium would provide 96% of the UL. The petitioner's recommended daily intake for children of 120 mg of magnesium would provide 48% of the UL for children of 4 years of age and above.

TOXICOLOGICAL DATA

Absorption, distribution, metabolism and excretion

Kinetics of magnesium aspartate.

Magnesium absorption depends on the status of magnesium stores in the body and is further dependent on the type of salt (inorganic or organic) and the formulation (capsule, tablet or granule) used. The bioavailability of magnesium from magnesium salts appears to be dependent on their water solubility. Organic salts of magnesium such as magnesium-L-aspartate and magnesium-L-lactate have the greatest water solubility and demonstrate a greater oral absorption and bioavailability compared to less soluble magnesium preparations such as magnesium oxide, magnesium hydroxide, magnesium carbonate and magnesium sulphate.

Clinical Pharmacokinetic Studies

The petitioner has provided two studies on the comparative bioavailability of magnesium from magnesium L-aspartate and other magnesium salts. These are summarised below.

Firoz & Graber (2001) compared the bioavailability of magnesium from magnesium L-aspartate, magnesium L-lactate, magnesium chloride and magnesium oxide in 16 healthy human volunteers (8 males and 8 females; age 25-55 years old). These volunteers were given approximately 90% of the Recommended Dietary Allowance (~300 mg) as a test preparations in a crossover design study, with each subject receiving each preparation (including 2 control periods) separated by a washout period of 3 days. Twenty-four hour urine samples were taken and bioavailability was measured as the increment of urinary magnesium excretion. Baseline rates of magnesium excretion were measured on two different days (one at the beginning and

one at the end). Subjects were asked to avoid high magnesium-containing foods and other magnesium supplements.

The results are summarised in Table 1.

Table 1 Urinary Magnesium Excretion following Administration of Magnesium L-aspartate, Magnesium L-lactate, Magnesium Chloride and Magnesium Oxide in Healthy Human Volunteers.

Preparation (dose)	**Urine Mg (mg/day) mean± SD**	**Δ from control (mg/day) mean± SD**	**p value***
Control	80.5± 24.5		
Mg Chloride (256 mg)	110.9± 37.5	30.4± 38.1	**0.007**
Mg Oxide (253.5 mg)	90.1± 33.7	9.6± 34.3	0.15
Mg Lactate (252 mg)	109.9± 43.5	29.4± 37.9	**0.006**
Mg Aspartate (260 mg)	105.3± 47.1	24.8± 44.1	**0.031**

*Student's t-test, paired comparison to control.

Magnesium chloride, magnesium aspartate and magnesium lactate displayed similar bioavailability. The bioavailability of magnesium from magnesium oxide was considerably lower (~2-fold) than from other magnesium forms. None of the subjects reported adverse gastrointestinal events at the doses administered.

Muhlbauer *et al*. (1991) compared the bioavailability of magnesium from two magnesium L-aspartate formulations (tablets and granules) and magnesium oxide (capsules) in 24 healthy human volunteers. The volunteers were separated into 3 groups of 8 (4 males and 4 females per group) and administered magnesium L-aspartate tablets, magnesium L-aspartate granules or magnesium oxide (capsules) according to a parallel group design. After a control (no treatment) and a placebo period of one week, 732 and 1098 mg (60 and 90 mEq/d respectively) magnesium were administered for 7 days each. The cumulative urinary excretion of magnesium was used to assess magnesium absorption.

The results are summarised in Table 2. The mean cumulative urinary magnesium excretion was similar during the control and placebo period, ranging from 77.5-93.7 mEq/ week. Urinary magnesium excretion was significantly increased with all three magnesium preparations. The cumulative urinary magnesium excretion following magnesium-L-aspartate administration either as tablets or granules was considerably greater than following the administration of magnesium oxide in capsules. There was no significant difference in cumulative urinary magnesium excretion following administration of tablets or granules of magnesium-L-aspartate. These results indicated higher absorption of magnesium-L-aspartate than magnesium oxide.

Table 2 **Total 7 Day Cumulative Urinary Magnesium Excretion (mEq/ 24h*7d) following Administration of Magnesium-L-aspartate or Magnesium Oxide in Healthy Human Volunteers.**

Preparation	**Control Days 0-7 (mEq/ 24h*7d)**	**Placebo Days 8-14 (mEq/ 24h*7d)**	**60 mEq/d Days 15-21 (mEq/ 24h*7d)**	**90 mEq/d Days 22-28 (mEq/ 24h*7d)**
Mg Aspartate Tablets	78 (54-101)	84 (59-110)	146 (108-184)	181 (137-225)
Mg Aspartate Granules	91 (61-120)	81 (56-106)	156 (113-199)	187 (151-224)
Mg Oxide Capsules	94 (76-111)	90 (74-105)	133 (111-155)	137 (115-159)

Mean (95% Confidence Intervals)
1 mEq is approximately equivalent to 12.2 mg Mg

All three preparations were well tolerated but with the higher dose (90 mEq/day ≈ 1098 mg Mg) of all preparations there was a small increase in stool frequency.

The authors concluded that magnesium-L-aspartate, in either tablet or granule form, demonstrated greater bioavailability of magnesium than magnesium oxide capsules in healthy volunteers.

Toxicity in laboratory animals

The Panel considered that there was no need to evaluate additional toxicology studies since the magnesium salts of L-aspartic acid are included on the positive list (Annex) in Directive 2001/15/EC as acceptable sources of L-aspartic acid for use in foods for special medical purposes.

Discussion

The Panel noted that the bioavailability of magnesium from magnesium L-aspartate was similar to that from other organic magnesium salts and the more soluble inorganic magnesium salts. The bioavailability magnesium from these salts was higher than that of magnesium oxide. The Panel noted that a number of magnesium compounds (acetate, carbonate, chloride, salts of citric acid, gluconate, glycerophosphate, salts of orthophosphoric acid, lactate, hydroxide, oxide and sulphate) were already permitted as sources of magnesium. The Panel noted that aspartate was used as an anion in other mineral compounds and was an amino acid normally found in the body.

Conclusions and Recommendations

The Panel concluded that the bioavailability of magnesium from magnesium L-aspartate was similar to that from other organic magnesium salts and the more soluble inorganic magnesium salts. The Panel concluded that the use of magnesium-L-aspartate as a source of magnesium in dietary foods for special medical purposes is not of safety concern at the proposed levels of

usage. The Panel concluded that there would be no safety concern from asparatate at the proposed usage levels.

Documentation provided to EFSA

Dossier prepared and submitted on behalf of the petitioner (Kora Healthcare) for the evaluation of magnesium aspartate as a new food additive (2004).
An annex containing a number of documents and publications (not all the papers and articles supplied have been referenced in the text as they include reviews and material that were not relevant to the safety assessment).
Relevant sections of the European Drug Master File (EDMF) on magnesium aspartate were provided in confidence to EFSA by the supplier (Boehringer Ingelheim) in support of the Technical Data section of the dossier.

References

Firoz M and Graber M.; (2001) Bioavailability of US Commercial Magnesium Preparations. Magnesium Research 14: 257-262

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SCIENTIFIC PANEL MEMBERS