European Food Safety Authority

The EFSA Journal (2008) 883, 1-23

SCIENTIFIC OPINION

Magnesium aspartate, potassium aspartate, magnesium potassium aspartate, calcium aspartate, zinc aspartate, and copper aspartate as sources for magnesium, potassium, calcium, zinc, and copper added for nutritional purposes to food supplements [1]

Scientific Panel on Food Additives and Nutrient Sources added to food (ANS)

(Question No EFSA-Q-2005-129, EFSA-Q-2006-260, EFSA-Q-2005-215, EFSA-Q-2005-101, EFSA-Q-2006-253, EFSA-Q-2006-294, EFSA-Q-2005-109, EFSA-Q-2006-282, EFSA-Q-2006-283, EFSA-Q-2006-284, EFSA-Q-2006-285, EFSA-Q-2006-305, EFSA-Q-2006-254, EFSA-Q-2005-161, EFSA-Q-2006-259)

Adopted on 27 November 2008

PANEL MEMBERS

F. Aguilar, U.R. Charrondiere, B. Dusemund, P. Galtier, J. Gilbert, D.M. Gott, S. Grilli, R. Guertler, G.E.N. Kass, J. Koenig, C. Lambré, J-C. Larsen, J-C. Leblanc, A. Mortensen, D. Parent-Massin, I. Pratt, I. Rietjens, I. Stankovic, P. Tobback, T. Verguieva, R. Woutersen.

SUMMARY

Following a request from the European Commission to the European Food Safety Authority (EFSA), the Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to provide a scientific opinion on the safety of magnesium aspartate, potassium aspartate, magnesium potassium aspartate, calcium aspartate, zinc aspartate, and copper aspartate added for nutritional purposes as sources of magnesium, potassium, calcium, zinc and copper in food supplements and on the bioavailability of magnesium, potassium, calcium, zinc and copper from these sources.

The present opinion deals only with the safety of magnesium aspartate, potassium aspartate, magnesium potassium aspartate, calcium aspartate, zinc aspartate, and copper aspartate as sources for magnesium, potassium, calcium, zinc, and copper, and with the bioavailability of the nutrient cations from these sources. The safety of magnesium, calcium, zinc, potassium

[1] For citation purposes: Scientific Opinion of the Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request from the Commission on magnesium aspartate, potassium aspartate, magnesium potassium aspartate, calcium aspartate, zinc aspartate, and copper aspartate added for nutritional purposes to food supplements. *The EFSA Journal* (2008) 883, 1-23.

and copper themselves, in terms of amounts that may be consumed, is outside the remit of this Panel.

The information on bioavailability provided to the Panel from the sourcess considered in this opinion allows one to conclude that calcium, magnesium, potassium and copper are bioavailable from these sources, with the exception of magnesium aspartate complex. In view of the reported information on the insolubility of the magnesium aspartate complex, the Panel could not consider the magnesium aspartate complex as bioavailable and thus could not evaluate exposure to aspartate arising from its consumption as a food supplement. In the case of zinc aspartate it is assumed that its reported solubility in diluted hydrochloric acid will allow its dissociation and absorption in the stomach. However, it was not clear to the Panel if further absorption could take place in the intestine considering its reported insolubility in water.

The Panel considers that the individual or combined use of zinc and copper aspartates as sources of zinc and copper, at the proposed use levels, are not of safety concern. However, the individual use of calcium, magnesium and potassium aspartates as food supplements, at the proposed use levels, could be of safety concern because the margins of safety towards a no observable adverse effect level (NOAEL) from a 90-day rat study are considered too low.

Furthermore, based on the cumulative exposure estimates arising from use of a multi-mineral combination, the Panel considers that the proposed use levels could be of safety concern given that the margin of safety between the estimated exposure and the NOAEL in the 90-day rat study is too low. Furthermore the estimated exposure would be above the levels reported to induce amino acid imbalance in intervention trials, taking into consideration aspartate exposure from the diet.

The Panel notes that according to Commission Regulation (EC) No 629/2008 the maximum levels of lead, mercury and cadmium in food supplements as sold should be 3 mg/kg, 0.1 mg/kg and 1 mg/kg, respectively.

Key words:

Food supplements, foods, magnesium aspartate dihydrate, magnesium potassium trihydrate, magnesium potassium tetrahydrate, magnesium potassium aspartate, calcium L-aspartate, calcium (II) hydrogen L-aspartate chloride dihydrate, zinc L-aspartate, potassium aspartate hemihydrate, monopotassium aspartate, monobasic monohydrate potassium aspartate, copper aspartate, CAS Registry Numbers: 2068-80-6, 28184-71-6, 7018-07-7, 92533-40-9, 19045-00-2, 36393-20-1, 14007-45-5, 1115-63-55.

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BACKGROUND AS PROVIDED BY THE COMMISSION

The European Community legislation lists nutritional substances that may be used for nutritional purposes in certain categories of foods as sources of certain nutrients.

The Commission has received requests for the evaluation of calcium aspartate, zinc aspartate, magnesium potassium aspartate, potassium aspartate, magnesium aspartate and copper aspartate added for nutritional purposes to food supplements

The relevant Community legislative measure is:

- Directive 2002/46/EC of the European Parliament and of the Council on the approximation of the laws of the Member States relating to food supplements (EC, 2002a)[2].

TERMS OF REFERENCE AS PROVIDED BY THE COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to provide a scientific opinion, based on its consideration of the safety and bioavailability of calcium aspartate, zinc aspartate, magnesium potassium aspartate, potassium aspartate, magnesium aspartate and copper aspartate added for nutritional purposes in food supplements

ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of the Working Group for the preparation of this opinion:

F. Aguilar, D. Boskou, D. Gott, S. Grilli, W. Grunow, R. Guertler, K. Hulshof, J.C. Larsen, J.C. Leblanc, C. Leclercq, W. Mennes, A. Mortensen, D. Parent-Massin, I. Pratt, I. Rietjens, P. Tobback, G. Speijers, F. Toldra.

[2] OJ No L 183, 12.7.2002, p. 51.

ASSESSMENT

1. Introduction

The present opinion deals only with the safety of magnesium aspartate, potassium aspartate, magnesium potassium aspartate, calcium aspartate, zinc aspartate, and copper aspartate as sources of magnesium, potassium, calcium, zinc, and copper, and with the bioavailability of the nutrient cations from these sources. The safety of magnesium, calcium, zinc, potassium and copper themselves, in terms of amounts that may be consumed, is outside the remit of this Panel.

2. Technical data

2.1. Identity of source

Aspartic acid is available with a variety of metals as complexes or salts. Aspartic acid is available either in its neutral form ($C_4H_7NO_4$, molecular weight 133 g/mol), as a monoanion ($C_4H_6NO_4^-$, molecular weight 132 g/mol), as a dianion ($C_4H_5NO_4^{2-}$, molecular weight 131 g/mol) or in an amino protonated form ($C_4H_8N^+O_4$, molecular weight 134 g/mol).

Calcium L-aspartate

Calcium L-aspartate was described by one petitioner as "calcium (II) hydrogen L-aspartate chloride dihydrate" or ***calcium L-aspartate hydrochloride dihydrate*** (Technical dossier, 2005d). The proposed molecular formula is $Ca(C_4H_5NO_4)\cdot HCl\cdot 2H_2O$, with a molecular weight of 243.7 g/mol, and CAS Registry Number 92533-40-9 (corresponding to the anhydrous form, L-aspartic acid calcium salt, hydrochloride (1:1:1)).

Another petitioner described calcium L-aspartate as "calcium di[(S)-2-aminohydrogenobutane-1,4-dioate]" or ***calcium di-L-aspartate*** (Technical dossier, 2005j). The molecular formula is $Ca(C_4H_6NO_4)_2$, with a molecular weight of 304.28 g/mol and CAS Registry Number 39162-75-9.

Magnesium L-aspartate

Magnesium L-aspartate was described by three petitioners as ***magnesium di-L-aspartate dihydrate*** (Technical dossier, 2005h, 2005i, 2007). The proposed molecular formula is $Mg(C_4H_6NO_4)_2\cdot 2H_2O$, with a molecular weight of 324.5 g/mol and CAS Registry Number 2068-80-6 (corresponding to the anhydrous form, L-aspartic acid magnesium salt (2:1)).

Another petitioner described magnesium L-aspartate as ***magnesium L-aspartate hydrochloride trihydrate*** (Technical dossier, 2005e). The proposed molecular formula is $Mg(C_4H_5NO_4)\cdot HCl\cdot 3H_2O$, with a molecular weight of 245.75 g/mol and CAS Registry Number 28184-71-6 (corresponding to the anhydrous form, magnesium L-aspartate hydrochloride (1:1:1)).

Another petitioner described magnesium L-aspartate as ***magnesium DL-aspartate tetrahydrate*** (Technical dossier, 2005g). The molecular formula is $Mg(C_4H_6NO_4)_2 \cdot 4H_2O$, with a molecular weight of 360.56 g/mol, and CAS Register Number 7018-07-7.

Another petitioner described magnesium L-aspartate as "magnesium aspartate complex 20 %", consisting of a mixture of 78 % magnesium aspartate and 22 % magnesium oxide (Technical dossier, 2005c). The Panel notice that this compound is different to other magnesium L-aspartates considered in this opinion.

Zinc L-aspartate

Zinc L-aspartate was described by one petitioner as "zinc [L-aspartate (2)-N,O_1,O_4]" or ***zinc L-aspartate*** (Technical dossier, 2005f). The molecular formula is $Zn(C_4H_5NO_4)$, with a molecular weight of 196.39 g/mol and CAS Registry Number 19045-00-2.

A second petitioner described zinc L-aspartate as ***zinc di-L-aspartate*** (Technical dossier, 2005l). The molecular formula is $Zn(C_4H_6NO_4)_2$, with a molecular weight of 329.58 g/mol and CAS Registry Number 36393-20-1.

Potassium L-aspartate

Potassium L-aspartate was described by one petitioner as ***monopotassium L-aspartate*** (Technical dossier, 2005b). The molecular formula is $K(C_4H_6NO_4^-)$, with a molecular weight of 171.19 g/mol and CAS Registry Number 1115-63-5.

A second petitioner described potassium aspartate as ***potassium L-aspartate hemihydrate*** (Technical dossier, 2005a). The proposed molecular formula is $K(C_4H_6NO_4)$ 1/2 H_2O, with a molecular weight of 180.29 g/mol and CAS Registry Number 14007-45-5 (corresponding to "L-Aspartic acid, potassium salt", where the number of potassium atoms (one or two) is not specified).

Another petitioner proposed ***potassium L-aspartate monohydrate*** (Technical dossier, 2005n). The proposed molecular formula is $K(C_4H_6NO_4) \cdot H_2O$, with a molecular weight of 189.21 g/mol. The CAS Registry Number provided, 1115-63-55, corresponds to the anhydrous form monopotassium L-aspartate.

Copper L-aspartate

Copper L-aspartate was described by one petitioner as ***copper(II) L-aspartate*** (Technical dossier, 2005m). The molecular formula is $Cu(C_4H_5NO_4)_2$, with a molecular weight of 327.73 g/mol. The CAS Registry Number was not given for this substance.

Magnesium potassium L-aspartate

Magnesium potassium L-aspartate was described by one petitioner as a mixture of magnesium aspartate and potassium aspartate (Technical dossier, 2005k). No chemical name, CAS Registry Number, molecular formula or molecular weight have been proposed by the petitioner for this substance.

2.2. Specifications

The specifications proposed by the petitioners are not homogenous and are summarised in the following tables.

Calcium L-aspartate is described as a white to off-white crystalline hygroscopic powder, being freely soluble in water (Technical dossier, 2005d, 2005j).

Table 1. **Chemical specifications proposed for calcium aspartate**

Technical dossier	Calcium content	Arsenic	Lead	Mercury	Heavy metals	Tapped bulk density
	% (w/w)	less than mg/kg				g/ml
2005d	12	1	3	n.i.	n.i.	0.3-1.0
2005j	13*	3	5	1	10	n.i.

*****theoretically calculated by ANS Panel based on 98 % purity; **n.i:** no information provided

Magnesium di-L-aspartate dihydrate is a white, crystalline powder or colourless crystals, freely soluble in water. It was described as containing 10-14 % water and 7.49 % magnesium based on theoretical calculations (Technical dossier, 2007).

Magnesium aspartate complex was described by one petitioner as a white to off-white powder, insoluble in water (< 1g/100 ml, 25°C), containing 20 % magnesium, and less than 5 mg/kg cadmium, less than 3 mg/kg arsenic and less than 10 mg/kg lead (Technical dossier, 2005c).

Magnesium L-aspartate hydrochloride trihydrate was described by one petitioner as a white powder, hydroscopic, freely soluble in water, showing a loss on drying of not more than 6 % (Technical dossier, 2005e).

Magnesium DL-aspartate tetrahydrate was described as a white crystalline powder or colourless crystal, easily soluble in water (40 g/l at 25°C), practically insoluble in ethanol, chloroform and benzene (Technical dossier, 2005g).

Magnesium potassium L-aspartate was described by one petitioner as a white to off-white powder, slightly hygroscopic, freely soluble in water (Technical dossier, 2005k).

Table 2. **Chemical specifications proposed for magnesium aspartate**

Technical Dossier	Magnesium content	Chloride	Sulfate	Ammonium	Iron	Arsenic	Lead	Mercury	Heavy metals	Cadmium	Tapped bulk density
	% (w/w)	less than mg/kg									g/ml
2007	7.49*	200	500	100	50	3	10	1	10	5	0.3-1.0
2005h	4**	200	500	100	50	n.i.	n.i.	n.i.	10	n.i.	n.i.
2005c	20	n.i.	n.i.	n.i.	n.i.	3	10	n.i.	n.i.	5	n.i.
2005e	8	n.i.	n.i.	n.i.	n.i.	1	3	n.i.	n.i.	n.i.	0.7-1.1
2005g	7*	200	500	200	30	n.i.	n.i.	n.i.	10	n.i.	n.i.
2005k	5.2-6	n.i.	n.i.	n.i.	n.i.	1	5	n.i.	n.i.	n.i.	n.i.

***** theoretically calculated by petitioner; ****** theoretically calculated by ANS Panel based on 100 % purity; **n.i**: no information provided

Zinc L-aspartate was described by one petitioner as a white crystalline powder, soluble in dilute hydrochloric acid and insoluble in water (Technical dossier, 2005f).

Table 3. **Chemical specifications proposed for zinc aspartate**

Technical dossier	Zinc content	Arsenic	Lead	Mercury	Heavy metals	Tapped bulk density
	% (w/w)	less than mg/kg				g/ml
2005f	27	1	5	n.i.	n.i.	0.8-1.2
2005l	20*	3	5	1	10	n.i.

***** theoretically calculated by ANS Panel based on 98 % purity; **n.i:** no information provided

Potassium aspartate is generally described as a white to off-white hygroscopic powder, odourless, with a characteristic taste, freely soluble in water and in dilute hydrochloric acid (Technical dossier, 2005a).

Table 4. **Chemical specifications proposed for potassium aspartate sources**

Technical dossier	Potassium content	Chloride	Sulfate	Ammonium	Arsenic	Lead	Mercury	Iron	Heavy metals	Cadmium	Tapped bulk density
	% (w/w)	less than mg/kg									g/ml
2005a	20	n.i.	n.i.	n.i.	1	5	n.i.	n.i.	n.i.	n.i.	0.5-1.0
2005b	21.9-23.7	210	280	500	1	n.i.	n.i.	20	10	n.i.	n.i.
2005n	20.7	n.i.	n.i.	n.i.	1	1	0.5	n.i.	n.i.	0.5	n.i.

n.i: no information provided

Copper aspartate was described as a blue crystalline powder, slightly soluble in water showing a loss on drying of not more than 6 % (at 250°C) (Technical dossier, 2005m).

The Panel notes that according to Commission Regulation (EC) No 629/2008 (EC, 2008) the maximum levels of lead, mercury and cadmium in food supplements as sold should be 3 mg/kg, 0.1 mg/kg and 1 mg/kg, respectively.

2.3. Manufacturing Process

The manufacturing processes have been adequately described by the petitioners.

2.4. Methods of analysis in food

Information on specific analysis in food was not provided. However, analytical methods for the general determination of calcium, magnesium, zinc, potassium and copper ions were given by the petitioners.

2.5. Reaction and fate in foods to which the source is added

No specific information on reaction and fate in foods was provided for the aspartate salts.

Calcium L-aspartate hydrochloride dehydrate was shown to be stable upon storage for 6 months at 75 % relative humidity and 40°C, as well as for 60 months at 60 % relative humidity and 25°C (Technical dossier, 2005d).

Magnesium L-aspartate hydrochloride trihydrate was shown to be stable upon storage for 6 months at 75 % relative humidity and 40°C, as well as for 60 months at 60 % relative humidity and 25°C (Technical dossier, 2005e).

Magnesium potassium L-aspartate was shown to be stable for 5 years upon storage at 40°C and 75 % relative humidity, as well as at 60 % relative humidity and 25°C (Technical dossier, 2005k).

Potassium L-aspartate hemihydrate was shown to be stable upon storage for 6 months at approximately 40°C and 75 % relative humidity , as well as for 60 months at approximately 25°C and 60 % relative humidity (Technical dossier, 2005a).

2.6. Case of need and proposed uses

Magnesium, magnesium potassium, calcium, zinc, potassium and copper aspartates are intended to be used as sources for magnesium, calcium, zinc, potassium and copper in food supplements.

2.7. Exposure

Not all petitioners proposed supplementation levels for the substances considered in this opinion; although the supplementation levels that were proposed were noted to differ considerably. Therefore the Panel decided to base its exposure estimations, when available, on the maximum supplementation levels proposed among petitioners, and when no information was available the Panel considered a supplementation level up to a defined reference value, such as a tolerable upper intake level.

Calcium L-aspartate

One petitioner proposed adding calcium aspartate to food supplements to supply up to 800 mg/day of calcium (Technical dossier, 2005j). Consequently the daily exposure to calcium aspartate, assuming calcium content of 12-13 %, would be approximately 6600 mg corresponding to approximately 5.8 g aspartate/day.

Magnesium L-aspartate

One petitioner proposed adding magnesium aspartate complex 20 % to food supplements in amounts up to 1000 mg/capsule without specifying the number of capsules recommended per day (Technical dossier, 2005c).

Another petitioner proposed to add magnesium di-L-aspartate dihydrate to supply up to 240 mg magnesium and 2600 mg of L-aspartic acid/day (Technical dossier, 2007).

A third petitioner proposed to supply up to 350 mg of magnesium di-L-aspartate dihydrate/day (Technical dossier, 2005i).

A fourth petitioner proposed to add magnesium di-L-aspartate dihydrate supplement to supply up to the tolerable upper intake level for magnesium of 250 mg/day (SCF, 2003) which would be equivalent to 6.25 g magnesium aspartate dihydrate[3] and accordingly to 6 g of aspartate (Technical dossier, 2005h).

Zinc L-aspartate

Addition of zinc di-L-aspartate to food supplements to supply up to 15 mg/day of zinc, as suggested by one petitioner (Technical dossier, 2005l) would result in a daily exposure to zinc aspartate, assuming mean zinc content of 24 %, of approximately 62 mg, corresponding to approximately 47 mg aspartate/day.

Potassium L-aspartate

One petitioner proposed adding potassium L-aspartate monohydrate to food supplements at doses between 200 and 750 mg/capsule, without specifying the number of capsules recommended per day (Technical dossier, 2005n). Data from the UK Food Standard Agency survey on the consumption of food supplements indicate that 24 % of adults (Henderson *et al*., 2002), 14 % of young people (Gregory, 2000) and 17 % of toddlers consume food supplements (Gregory, 1995). The use among high consumers (97.5th percentile) ranged from 2 units/day (data do not discriminate between tablets or capsules) in young people to 7 units/day in adults. Taking into account the proposed supplementation, these values would correspond to an exposure estimate of 400-1500 and 1400-5250 mg of potassium aspartate/day in young people and adults, respectively. Accordingly, assuming mean potassium content of approximately 21 % in potassium aspartate, the exposure to aspartate from these sources would be around 0.3-1.1 and 1-4 g in young people and adults, respectively.

Copper aspartate

Addition of copper aspartate to food supplements to supply up to 2 mg/day of copper (Technical dossier, 2005m) was proposed by one petitioner, who stated that this amount would be equivalent to 10.3 mg copper L-aspartate. Consequently, the daily exposure of aspartate from this source would be approximately 8 mg/day.

Overall aspartate intake

By adding up maximum exposures calculated for individual aspartate sources considered in this opinion, the Panel estimated the potential exposure to aspartate from a multi-mineral

[3] assuming a magnesium content of 4 %

mixture of magnesium, calcium, zinc, potassium and copper aspartates to be up to approximately 16 g/day[4].

Aspartic acid exposure from diet

Aspartic acid is an non-essential (dispensable) amino acid present in protein-rich foods and is the second most abundant amino acid found in several foodstuffs, after glutamic acid (USDA ARS, 2007). There are only a few food composition tables available that provide information on aspartic acid content in foods. The aspartic acid content reported in meat and meat products is 0.8-2.6 g/100 g in beef, 0.6-2.4 g/100 g in pork, 0.6-1.9 g/100 g in lamb, 1.8-2.3 g/100 g in chicken, 1.1-2.6 g/100g in fish and seafood. Values of 1.2-2.9 g/100 g have been reported in cheese and 1.3-1.5 g/100 g in eggs. The content of aspartic acid in cereals and cereal products varies from approximately 0.2 to 1.3 g/100 g. The aspartic acid content of fruit and vegetables is generally low (Møller *et al.*, 2005; Paul *et al.*, 1980; Souci *et al.*, 2002; USDA, 2007).

The Institute of Medicine (IOM) reported that based on US data from the Third National Health and Nutrition Examination Survey (NHANES III; dietary data obtained by means of 24 h recalls and food frequency in a nationwide sample of approximately 34000 people), the mean intake of aspartic acid ranged from 4.1 g/day (children 1-3 year old) to 9.3 g/day (males 19-30 year old). At the 95th percentile aspartic acid intakes ranged from 6.6 g/day (children 4-8 year old) to 12.9 g/day (males 19-50 year old) (IOM, 2005).

2.8. Information on existing authorisations and evaluations

In the European Community several calcium, magnesium, zinc, potassium and copper organic and inorganic salts are authorised sources of minerals for specific nutritional purposes in foods for particular nutritional uses, notably in foods for special medical purposes (EC, 2001; EC 2006). Furthermore, calcium, magnesium and potassium salts of L-aspartic acid are also acceptable sources of L-aspartic acid for use in the same foods as described before (EC, 2001).

The Scientific Committee on Food (SCF) considered that the L-aspartic acid salts of calcium, potassium and magnesium could be safely used as sources of L-aspartic acid in foods for particular nutritional purposes (SCF, 1999).

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Foods (AFC) evaluated magnesium aspartate as a mineral substance used as a source of magnesium in dietary foods for special medical purposes (EFSA, 2005a). It was concluded that the use of magnesium L-aspartate, as a source of magnesium in dietary foods for special medical purposes, was not of safety concern at the proposed levels of usage and that there would be no safety concern from aspartate at the proposed usage levels. The daily exposure levels evaluated in that opinion were equivalent to approximately 240 mg of magnesium and 2600 mg of L-aspartic acid for adults.

The SCF considered the use of L-aspartic acid magnesium salt to be acceptable for use in the manufacture of foods for particular nutritional purposes (SCF, 1999).

[4] 5.8 g + 6 g + 0.047 g + 4 g + 0.008 g = 15.85 g

Sodium and potassium salts of L-aspartic acid may be used as amino acid nutrients added to foods in the United States (Federal Register, 2004).

The SCF and the US Food and Nutrition Board (FNB) have stressed that caution should be warranted when using any single amino acid at levels significantly above those normally found in food, which could lead to nutritional imbalances (SCF, 1990; IOM, 2005).

There are neither upper tolerable intake level nor required intakes set for aspartic acid (IOM, 2005; WHO, 2002). In 2002, the IOM noted that supplementation of up to 8 g/day of aspartic acid in addition to approximately 3 g/day from food did not result in any documented adverse effects (IOM, 2002).

The World Health Organization (WHO) expert consultation on protein and amino acid requirements in human nutrition considered that for dispensable amino acids (which includes aspartic acid) 0.48 g/kg bw/day should be sufficient to maintain body nitrogen homeostasis in healthy adults (WHO 2002). For a 60 kg individual, this amount would be equivalent to 29 g/day.

3. Biological and toxicological data

3.1. Bioavailability

Bioavailability of magnesium from magnesium aspartates

In its evaluation in 2005, the AFC Panel concluded that in humans the bioavailability of magnesium from magnesium L-aspartate was similar to that from other organic magnesium salts and the more soluble inorganic magnesium salts (EFSA, 2005a). Overall, it was concluded that organic salts of magnesium 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.

The bioavailability of magnesium from ten organic and inorganic salts, including magnesium aspartate, was assessed in rats using a stable isotope approach (Coudray *et al*., 2005). Ten groups of eight male magnesium-depleted Wistar rats (6 weeks old) were fed for two weeks a diet containing 550 magnesium/kg (target magnesium level of 600 mg/kg diet) either as aspartate, oxide, chloride, sulphate, carbonate, acetate, pidolate, citrate, gluconate or lactate salt. After 10 days of treatment the animals received, by gavage, a dose of 1.8 mg of ^{26}Mg as $MgCl_2$ (showing the stable isotopes ^{24}Mg = 2.33 %, ^{25}Mg = 1.28 %, ^{26}Mg = 96.38 %) . The magnesium isotope ratios were determined in faeces and urine collected for 4 consecutive days. Magnesium levels were also determined in plasma, bones and erythrocytes of the animals. Magnesium was found to be bioavailable from all sources tested. Overall, magnesium absorption and retention values ranged from 51 to 67 % and from 39 to 49 %, respectively. Magnesium gluconate showed the highest magnesium absorption and retention values (approximately 67 and 49 %, respectively), followed by magnesium aspartate (approximately 60 % and 47 %, respectively) and magnesium lactate (approximately 59 % and 48 %, respectively). In general, magnesium from organic magnesium salts was slightly more bioavailable than magnesium from inorganic salts in this study. None of the treatments

affected body weight gain, pH or magnesium solubility in the small and large intestine or in the caecum.

The bioavailability of magnesium from magnesium DL-hydrogen aspartate was compared to that of magnesium D-gluconate by measuring its renal clearance in eighteen healthy male volunteers aged 23 to 35 years in a cross-over 13-day study (Kuhn *et al.*, 1992). During the study subjects received a magnesium-rich diet to saturate their magnesium pool so that the excreted magnesium measured after treatment would reflect absorbed amounts. Volunteers were administered at random either 5 mg of magnesium DL-hydrogen aspartate (assuming a magnesium content of 7 % - as referred by one petitioner this amount would be equivalent to approximately 4.6 mg aspartate) or 5 mg of magnesium D-gluconate. Magnesium concentrations were measured in serum at several time points and in 24 h urine samples. Magnesium bioavailability was defined as the percentage of cumulative amount of magnesium eliminated in urine relative to the administered dose. The areas under the curves of magnesium concentrations in blood were similar in both treatments. Magnesium from magnesium DL-aspartate showed slightly higher renal elimination values between treatments, but no statistically significant differences were observed. Magnesium bioavailability from magnesium DL-hydrogen aspartate was estimated to be approximately 44 % and from magnesium D-gluconate 42 %.

No specific bioavailability studies were made available on magnesium potassium aspartate. It was thus considered that since this salt is freely soluble in water, it will be dissociated to their corresponding ions in the gastrointestinal tract, being expected to behave similarly in terms of bioavailability, as other sources of magnesium and potassium in the diet.

No specific bioavailability studies were made available on magnesium aspartate complex. This complex was reported by the petitioner to be less soluble in water than the other sources of magnesium considered in this opinion and thus it can be anticipated to have lower bioavailability than other soluble sources of magnesium in the diet.

Bioavailability of calcium, potassium, zinc and copper from calcium, potassium, zinc, and copper aspartates

No specific bioavailability studies were made available on these aspartate salts. It was thus considered that since these salts, with the exception of magnesium aspartate complex, are freely soluble in water or in diluted hydrochloric acid solutions, they will dissociate to their corresponding ions in the gastrointestinal tract. It can thus be anticipated that these compounds will have similar bioavailability to other soluble sources of the salts in the diet. For zinc aspartate, it was assumed that its reported solubility in diluted hydrochloric acid will allow its dissociation and absorption in the stomach, although it was not clear if further absorption could take place in the intestine considering its reported insolubility in water.

3.2. Metabolic fate of the source and biological distribution

The absorption and metabolic fate of calcium, magnesium, zinc, potassium and copper cations has been thoroughly described previously by SCF and EFSA (SCF, 1993; 2001; 2003a,b,c; EFSA, 2005b), compiled in EFSA 2006 (EFSA, 2006).

L-aspartic acid is a constituent of peptides and proteins and can be a precursor for synthesis of purines and pyrimidines, it can also enter the systemic circulation and be distributed to various tissues of the body, including the brain. In mammals L-aspartic acid is a non-essential amino acid formed by the transamination of oxaloacetate. L-aspartate is absorbed from the small intestine by an active transport process and is transported to the liver via the portal circulation. During intestinal passage and in the liver aspartate is metabolised among other substances to amino acids such as alanine, proline, L-arginine and glutamic acid. No data was provided on metabolic fate of D-aspartic acid.

Oral administration by gavage to Wistar rats (7, 21 and 35 days old) of 1.9 and 3.8 g potassium aspartate[5]/ kg body weight, slowly increased plasma aspartate levels reaching a maximum of 30 to 90 min after administration (44 and 98 µmoles/100 ml, respectively) (Itoh *et al.* 1979). Control aspartate plasma levels (~ 3 µmoles/100 ml) were attained 4 hours after administration. An age-dependent response on the maximum plasma concentration levels was observed with both treatments (35>21>>7 days old rats).

Due to a slower absorption of aspartate in comparison to other amino acids in humans and due to the preferential transamination in the gut of absorbed aspartate, there is almost no change in aspartate plasma levels after ingestion (Anderson and Raiten, 1992). Ingestion of a single dose of 10 g aspartate by nine healthy subjects increased the plasma aspartate level by 40 µmole/l only (Carlson *et al.*, 1989). Moreover, nine healthy young adults consumed 15 g L-arginine L-aspartate/day over a period of four weeks, their aspartate levels in plasma were not significantly higher than in 12 placebo subjects (Gremion *et al.*, 1989).

3.3. Toxicity data

No specific toxicological data was provided on any aspartate salt considered in the present opinion.

Animal Data

According to Classen, unpublished toxicology data shows LD_{50} values of 6.8, 6.9 and 4.5 g magnesium L-aspartate hydrochloride/kg bw in rats, mice and dogs, respectively (Classen, 2002). Repeated dose toxicity studies in rats and dogs reported in this publication (exact dosage and duration of treatment not given) showed mild reversible diarrhoea in both species, emesis in dogs and reduced gain of body weight in both species. It is mentioned that reproduction studies performed on rats under a Mg-deficient diet enriched with increasing concentrations of magnesium L-aspartate hydrochloride (dosage not given) showed foetal toxicity characterised by decreased body weight gain and decreased magnesium and calcium content of the skeleton of the offspring. However, it was reported that in thalidomide-sensitive New Zealand rabbits no teratogenic potential in the offspring was produced at doses up to 1710 mg magnesium L-aspartate/kg bw (assuming a magnesium content of 4 %, this amount would be equivalent to approximately 1.6 g of aspartate). It was also reported that no mutagenic potential was identified in standardized Ames tests with 5 test strains, with and without metabolic activation, and in the micronucleus test in mice (Classen, 2002).

Human Data

[5] expressed as aspartic acid

No significant changes were reported in haematology, clinical chemistry, electrocardiograms or urine analysis done on 18 healthy male volunteers aged 23 to 35 years receiving a magnesium-rich diet and supplemented with 5 mg of magnesium DL-hydrogen aspartate/day for 13 days (assuming a magnesium content of 7 % as referred by one petitioner, this amount would be equivalent to approximately 4.6 mg aspartate) (Kuhn *et al.*, 1992).

In a double blind placebo controlled study from the 1960s, on 145 patients suffering from fatigue aged 15 to 70 years old, 66 patients taking 8 tablets a day each containing 500 mg of potassium and magnesium salts of aspartic acid per tablet (equivalent to up to 4000 mg per day), for 18 months, no adverse side effects were reported (Hicks, 1964). Assuming minimum magnesium content of 4 % this amount would be equivalent to approximately 3.8 g aspartate/day for 18 months.

Aspartic acid

Animal data

In animals aspartic acid toxicity has been reported to resemble that of glutamic acid (Garlick, 2004). Hypothalamic lesions were also reported in infant mice and rats after administration of relatively large doses of aspartate salts or aspartic acid.

Oral administration by gavage of 1.9 and 3.8 g potassium aspartate/kg bw (assuming a mean potassium content of 20 %, this dosage would be equivalent to approximately 1.5 and 3.0 g aspartate/ kg bw, respectively) of at least 5 male Wistar rats to groups of animals aged 7, 21 and 35 days old, did not affect free amino acids levels in plasma except for aspartic acid, glutamic acid, alanine and proline (Itoh *et al.*, 1979). It was reported that oral administration of 3.8 g potassium aspartate/kg bw, leading to aspartate plasma levels of 66 µmoles/100 ml, induced hypothalamic lesions in 50 % of the 7-days old rats group. Aspartate plasma levels of 90 and 194 µmoles/100 ml were reported to induce those lesions observed in 50 % of the 21- and 35-days old rat groups, respectively. In this study no histopathological findings on the hypothalamus were reported in animals infused intravenously with similar doses of potassium aspartate. It was suggested that elevated plasma levels of aspartate and glutamate, could be the factors inducing neuronal damage in this assay.

Subcutaneous administration of L-aspartic acid to four Swiss albino mice litters at doses of 15 mmole/kg bw for four days induced the same neuronal lesions and manifestations as those reported after administration of monosodium glutamate (Schainker and Olney, 1974). Administration of a related amino acid (DL-aminoadipic acid) lacking neuroexcitatory properties did not show any of these effects. Neurotoxic effects attributed to neurotransmitter amino acids such as glutamate have not been reported in other tested species. Furthermore, according to Garlick (2004) administration to humans of 75 to 130 mg aspartic acid/kg bw/day (equivalent to approximately 4.5 and 8 g for a 60 kg individual), as a supplement during short or prolonged exercise regimes, did not induce adverse effects.

In a recent 90-day feeding study, 110 Fischer 344 rats (55 males and 55 females) were divided randomly into 5 treatment groups and fed diets controlled for L-aspartic content (Tada *et al.* 2008). Dietary L-aspartic acid dosing was 0, 0.05, 1.25, 2.5 and 5.0 %, corresponding to 0, 28.7, 715.2, 1470.2 and 2965.9 mg/kg bw/day for females and to 0, 26.9, 696.6, 1416.6 and 2770.2 mg/kg bw/day for males. Parameters evaluated included body-weight and food consumption, in-life and gross necropsy observations, clinical chemistry, haematology, and urinalysis, organ weights and extensive histology. No statistically

significant differences on food consumption or average body-weights were reported in rats of both sexes. Statistically significant differences compared to controls were reported in serum total cholesterol, triglycerides, blood urea nitrogen and creatinine values in both sexes. However, except for values for total cholesterol and triglycerides in males, the other reported changes were not dose-related and were within historical control values, according to the authors. In male rats, increased relative weights of the heart and kidneys were reported in the 1.25 and 5.0 % exposed groups, respectively. No such changes were reported in females. Histopathological findings were unchanged for most tissues and organs examined (including the brain) except for an apparent dose-related regenerative renal tubules dilation in males accompanied by inflammatory cell infiltration, albeit only statistically significant at the 2.5 and 5.0 % doses. Immunohistochemistry results of kidney sections discarded α2u-globulin related renal injury, and these effects were thus related to the treatment. Acinar cell hypertrophy of submandibular and parotid glands were also observed in both sexes particularly in those exposed to the highest dose (5.0 %), albeit this was not dose-related. No signs or symptoms of neurotoxicity were observed at any of the doses tested. A NOAEL of approximately 700 mg/kg bw/day for males was identified based on renal toxicity findings, taking into consideration that kidney histopathological changes were only statistically significant from the 2.5 % exposed male rats group. The Panel notes that reported exposure estimates from dietary intake of aspartic acid are 3 times lower than this NOAEL (216 mg/kg bw/day versus 700 mg/kg bw/day).

Human data

Numerous intervention trials have been performed in adults with different aspartate compounds (sodium, magnesium, potassium-magnesium, buffered aspartic acid, arginine aspartate) in doses ranging from 1 to 10 g/day, for time periods between one single dose and four weeks, mostly for the purpose of enhancing muscular strength, endurance and/or performance or for reducing exercise-induced hyperammonaemia and lactate production in sports people. None of these studies was done to assess toxicity of aspartate intake, however, excluding reports on plasma amino acid imbalance and soft stools/diarrhoea, no other adverse effects were reported (Colombani *et al*., 1999; Chouinard *et al*., 1990).

Consumption of 15 g of arginine aspartate daily, corresponding to 6.3 g L-aspartate, over 14 days in a double-blind, placebo-controlled cross-over trial by 14 endurance-trained runners resulted in significantly higher plasma levels of arginine, ornithine and urea as compared to placebo. In contrast, plasma levels of most other amino acids, including aspartic acid, and total amino acids were reduced (Colombani *et al*., 1999).

4. Discussion

When considering aspartate sources individually, the levels of exposure estimated in this opinion amount up to 6 g/day for calcium aspartate (equivalent to 100 mg/kg bw/day for a 60 kg individual), 5.8 g/day for magnesium aspartate (equivalent to 97 mg/kg bw/day), 4 g/day for potassium aspartate (equivalent to 67 mg/kg bw/day), 0.05 g/day for zinc aspartate (0.8 mg/kg bw/day) and 0.008 g/day for copper aspartate (0.1 mg/kg bw/day). These values are all below those reported to induce amino acid imbalance in intervention trials (6.3 g aspartate/day) and they are, respectively, 7, 7.2, 10.5, 875 and 7000 times lower than the

NOAEL for aspartate identified from a 90-day rat study. Based on these margins of safety, the Panel concludes that the use of zinc and copper aspartate, as sources of zinc and copper at the proposed use levels, are not of safety concern but that the use of calcium, magnesium and potassium aspartate could be of safety concern because the margins of safety are considered too low.

The Panel notes that if all sources would be used simultaneously, combined exposure will be 16 g/day (equivalent to 267 mg/kg bw/day), which is above the reported amounts inducing amino acid imbalance in intervention trials (6.3 g/day). Furthermore, this value is only 3 times lower than the NOAEL from the rat study and due to the low margin of safety the Panel considers this of safety concern.

The Panel estimates that the exposure to aspartate from these food supplements should be added to the aspartate exposure arising from the diet.

Based on US data, estimates of the mean exposure to aspartic acid arising from the diet are 4.1 g/day (children 1-3 year old) to 9.3 g/day (males 19-30 year old) and at the 95th percentile 6.6 g/day (children 4-8 year old) to 12.9 g/day (males 19-50 year old). Under these conditions, estimates of maximum daily exposure to aspartate ions from the diet (13 g/day) and from calcium or magnesium aspartate supplements would be approximately 19 g/day[6], and from potassium aspartate would be 17 g/day[7]. Aspartate exposure estimates from zinc or copper supplementation would not significantly change aspartate exposure from the diet.

Taken individually these levels of exposure are lower than those reported to induce amino acid imbalance in intervention trials, when aspartate exposure from the diet is also taken into consideration (19.3 g/day)[8]. However, when considering the potential total intake of aspartic ions arising from the diet and from a potential multi-mineral combination of all food supplements the exposure could add up to 29 g/day[9] . In line with the SCF concerns, the Panel considers that the use of L-amino acids in food supplements should not give rise to a nutritional imbalance of the amino acids. Thus the Panel concludes that under these conditions aspartate ion exposure from a multi-mineral combination of this type could be of safety concern.

CONCLUSIONS

The present opinion deals only with the safety of magnesium aspartate, potassium aspartate, magnesium potassium aspartate, calcium aspartate, zinc aspartate, and copper aspartate as sources of magnesium, potassium, calcium, zinc, and copper, and with the bioavailability of the nutrient cations from these sources. The safety of calcium, magnesium, potassium, zinc and copper itself, in terms of amounts that may be consumed, is outside the remit of this Panel.

The information on bioavailability provided to the Panel from the sourcess considered in this opinion allows one to conclude that calcium, magnesium, potassium, zinc and copper are bioavailable from most of the sources, with the exception of the magnesium aspartate complex source. In view of its reported insolubility, the magnesium aspartate complex source

[6] 6 g from aspartate supplementation + 13 g aspartate from the diet
[7] 4 g from potassium supplementation + 13 g aspartate from the diet
[8] 6.3 g from Colombani et al. + 13 g aspartate from the diet
[9] 16 g multi-mineral combination + 13 g aspartate from the diet

proposed for use in food supplements in this opinion could not be considered as its bioavailability and its potential aspartate exposure could not be evaluated. For zinc aspartate it has been assumed that its reported solubility in diluted hydrochloric acid will allow its dissociation and absorption in the stomach although it was not clear to the Panel if further absorption could take place in the intestine considering its reported insolubility in water. The Panel considers that the individual or combined use of zinc and copper aspartates as sources of zinc and copper, at the proposed use levels, are not of safety concern. However, the individual use of calcium, magnesium and potassium aspartates as food supplements, at the proposed use levels, could be of safety concern because the margins of safety towards a NOAEL from a rat study are considered too low.

Furthermore, based on the cumulative exposure estimates arising from use of a multi-mineral combination, the Panel considers that the proposed use levels could be of safety concern given that the margin of safety between the estimated exposure and the NOAEL in the 90-day rat study is too low. Furthermore the estimated exposure would be above the levels reported to induce amino acid imbalance in intervention trials, taking into consideration aspartate exposure from the diet.

The Panel notes that according to Commission Regulation (EC) No 629/2008 the maximum levels of lead, mercury and cadmium in food supplements as sold should be 3 mg/kg, 0.1 mg/kg and 1 mg/kg, respectively.

DOCUMENTATION PROVIDED TO EFSA

1. Technical dossier on potassium aspartate. July 2005a. Submitted by Sami Labs Limited. Bangalore, India.
2. Technical dossier on potassium aspartate. July 2005b. Submitted by Solgar Vitamin & Herb. Aldbury, England.
3. Technical dossier on magnesium–L–aspartate. March 2005c. Submitted by ProMedico – Pewa Med HandelsgmbH. Graz, Austria.
4. Technical dossier on calcium aspartate. September 2005d. Submitted by Sami Labs Limited. Bangalore, India.
5. Technical dossier on magnesium aspartate. July 2005e. Submitted by Sami Labs Limited. Bangalore, India.
6. Technical dossier on zinc aspartate. July 2005f. Submitted by Sami Labs Limited. Bangalore, India.
7. Technical dossier on DL-magnesium-aspartate-tetrahydrate. February 2005g. Submitted by Gradiens Ltd. Budapest, Hungary.
8. Technical dossier on magnesium L-aspartate. May 2005h. Submitted by Health Food Manufacturer's Association. Surrey, England.
9. Technical dossier on magnesium L-aspartate. June 2005i. Submitted by Kiwi Farm b.v. Katwijk, Nederland.
10. Technical dossier on calcium L-aspartate. May 2005j. Submitted by Health Food Manufacturers Association. Surrey, England.

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GLOSSARY / ABBREVIATIONS

ANS	Scientific Panel on Food Additives and Nutrient Sources added to Food
AFC	Scientific Panel on food additives, flavourings, processing aids and materials in contact with food.
bw	body weight
CAS	Chemical Abstract Service
EFSA	European Food Safety Authority
IOM	Institute of Medicine
NDA	Scientific Panel on Dietetic Products, Nutrition and Allergies
NOAEL	No-Observed-Adverse-Effect Level
SCF	Scientific Committee on Food