

## SCIENTIFIC OPINION

### **Calcium ascorbate, magnesium ascorbate and zinc ascorbate added for nutritional purposes in food supplements<sup>1</sup>**

#### **Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food**

(Question No EFSA-Q-2006-229, EFSA-Q-2005-087, EFSA-Q-2005-104)

**Adopted on 24 February 2009 by written procedure**

#### **PANEL MEMBERS**

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#### **SUMMARY**

Following a request from the European Commission to the European Food Safety Authority, the Scientific Panel on Food Additives and Nutrient Sources added to Food has been asked to provide a scientific opinion on the safety of calcium ascorbate, magnesium ascorbate and zinc ascorbate added for nutritional purposes to food supplements as sources of calcium, magnesium, zinc and vitamin C, and on the bioavailability of the nutrient cations from these sources as well as the vitamin C bioavailability from magnesium ascorbate and zinc ascorbate.

Several calcium, magnesium and zinc salts are authorised sources of minerals in foods for specific nutritional purposes (Directive 2001/15/EC). Calcium ascorbate is an approved food additive (E 302) (Directive 1995/2/EC) and an approved source of vitamin C in food supplements and in foods for specific nutritional purposes (Directive 2001/15/EC and Directive 2002/46/EC).

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<sup>1</sup> For citation purposes: Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food on a request from the Commission on magnesium ascorbate, zinc ascorbate and calcium ascorbate added for nutritional purposes in food supplements. *The EFSA Journal* (2009) 994, 1-22.

Based on the considerations of dissociation in the gastrointestinal tract, the Panel considers that the bioavailability of calcium, magnesium, zinc and ascorbic acid from these sources is expected to be comparable to their bioavailability from other dissociable salts which are permitted sources of these nutrients in food supplements.

The Scientific Committee on Food (SCF) evaluated calcium ascorbate (E 302) as a food additive (1989) and the European Food Safety Authority evaluated it as a food supplement source of vitamin C in 2004. The SCF established Tolerable Upper Intake Levels for magnesium and zinc in 2001 and 2003, respectively. Therefore, no further toxicological evaluations of calcium ascorbate, magnesium ascorbate and zinc ascorbate are needed for this present opinion.

The total exposure to calcium of users of calcium ascorbate at the use and use levels proposed by the petitioner (up to 1500 mg calcium ascorbate/person/day, which corresponds to 141 mg/day calcium and to 1232 mg/day vitamin C) will not exceed the Tolerable Upper Intake Level of 2500 mg/person/day for calcium established for adults by the SCF. The additional exposure to vitamin C of users of calcium ascorbate at the use and use levels proposed by the petitioner will be below the amounts which may give rise to acute gastrointestinal symptoms (3-4 g/person/day).

The additional exposure to magnesium, of magnesium ascorbate users at the use and use levels proposed by the petitioner (up to 1120.8 mg/person/day, which corresponds to 70 mg/day magnesium and 1000 mg/day vitamin C), will not exceed the Tolerable Upper Intake Level of 250 mg/person/day, established by the SCF, for readily dissociable magnesium salts, which is based on a no-observed-adverse-effect-level (NOAEL) for mild transient laxative effects in humans. This Tolerable Upper Intake Level refers to supplemental magnesium, taken in addition to magnesium present in normal food and beverages, and holds for adults including pregnant and lactating women and children from four years on. The additional exposure to vitamin C of users of magnesium ascorbate is at a level not associated with adverse gastrointestinal effects.

For zinc ascorbate, as a source of zinc at the use and the use levels proposed by the petitioner (up to 66.5 mg zinc ascorbate/person/day, which equates to 10 mg of zinc and to 54 mg vitamin C), the anticipated total mean exposure to zinc from food and food supplements will not exceed the Tolerable Upper Intake Level of 25 mg/person/day established by SCF in 2002 for adults and pregnant and lactating woman, and children from 15 years of age. For children below the age of 15 years, the anticipated total mean exposure may exceed the Tolerable Upper Intake Levels. At the 97.5<sup>th</sup> percentile of zinc intake from the diet, the Tolerable Upper Intake Level for zinc will be exceeded for adults and children of all age groups. The additional exposure to vitamin C of users of zinc ascorbate is at a level not associated with any adverse gastrointestinal effects.

The Panel notes that the exposure to vitamin C from all the three sources at the use and use levels proposed by the petitioners will be 2283 mg/person/day. This amount may be associated with an increased risk of adverse gastrointestinal effects. The acute gastrointestinal effects may occur at higher intakes (3-4 g/person/day).

The Panel concludes that the bioavailability of calcium, magnesium or zinc from the ascorbates, and of vitamin C from the magnesium or zinc ascorbates, is not expected to differ from that of already permitted sources of calcium, magnesium, zinc, and vitamin C for food supplements.

The Panel concludes that the use of calcium ascorbate as a source of calcium, and of magnesium ascorbate as a source of magnesium and vitamin C in food supplements, at the use levels proposed by the petitioners, is not of safety concern.

The Panel concludes that the use of zinc ascorbate as a source of zinc and vitamin C in food supplements is not of safety concern. However the Panel is concerned that when the dietary intake is also taken into consideration, in the case of food supplements providing 66.5 mg zinc ascorbate or above, the Tolerable Upper Intake Level for zinc established by the SCF will be exceeded.

**Key words:**

Food supplements, calcium ascorbate, CAS No 5743-28-2, magnesium ascorbate, CAS No 15431-40-0, zinc ascorbate, CAS No 151728-40-4.

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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 a request for the evaluation of magnesium ascorbate, zinc ascorbate and calcium ascorbate 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<sup>2</sup>.

## 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 magnesium ascorbate, zinc ascorbate and calcium ascorbate added for nutritional purposes in food supplements.

## ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of the Working Group A on Food Additives and Nutrient Sources of the ANS Panel for the preparation of this opinion: F. Aguilar, N. Bemrah, P. Galtier, J. Gilbert, S. Grilli, R. Guertler, G.E.N. Kass, C. Lambré, J.C. Larsen, J.-C. Leblanc, A. Mortensen, I. Pratt, I. Stankovic.

The Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) would like to thank E. Konings (Seconded National Expert of the DATEX Unit) for his contribution to the preparation of this opinion.

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<sup>2</sup> OJ L 183, 12.7.2002, p.51.

## ASSESSMENT

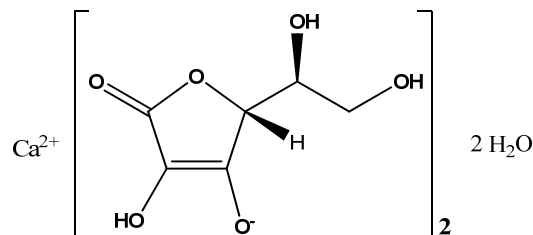
### 1. Introduction

The present opinion deals only with the safety of calcium ascorbate as a particular source of calcium, magnesium ascorbate as a particular source of magnesium and vitamin C, of zinc ascorbate as a particular source of zinc and vitamin C, and with the bioavailability of the nutrient cations from these sources as well as the vitamin C bioavailability from magnesium ascorbate and zinc ascorbate.

### 2. Technical data

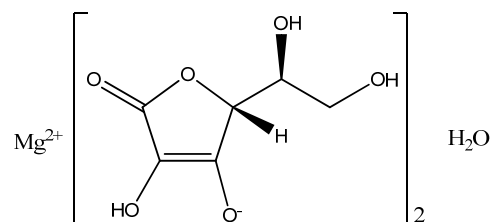
#### 2.1. Chemistry

The chemical name of **calcium ascorbate dihydrate** according to IUPAC nomenclature is calcium di[(R)-2-[(S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate] dihydrate. The compound has the CAS Registry Number 5743-28-2, molecular weight of 426.4 g/mol, the molecular formula  $C_{12}H_{14}O_{12}Ca \cdot 2H_2O$  and it has the following structural formula:



**Magnesium ascorbate monohydrate** is referred to by the petitioner as an ascorbic acid, magnesium salt (2:1) with a molecular weight of 392.56 g/mol and the molecular formula  $C_{12}H_{14}O_{12}Mg \cdot H_2O$ . The CAS Registry Number provided by the petitioner, 15431-40-0, corresponds to the anhydrous form.

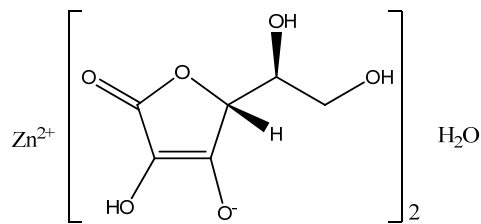
The structural formula is:



Synonyms of magnesium ascorbate are “L-ascorbic acid, magnesium salt” or “magnesium ascorbate, monohydrate”.

**Zinc ascorbate monohydrate** is referred to by the petitioner as an ascorbic acid, zinc salt with a molecular weight of 433.64 g/mol, and the molecular formula  $C_{12}H_{14}O_{12}Zn \cdot H_2O$ . The CAS Registry Number provided by the petitioner, 151728-40-4, corresponds to the anhydrous form.

The structural formula is:



Synonym of zinc ascorbate are “L-ascorbic acid, zinc salt” and “zinc ascorbate, monohydrate”.

## 2.2. Specifications

### Calcium ascorbate

The Panel notes that the specifications for calcium ascorbate as a food additive are defined in Directive 2008/84 (EC, 2008a).

The petitioner presented a United States Pharmacopoeia (USP) specification for calcium ascorbate as such, and for a preparation of calcium ascorbate, 97 % from direct compression. This formulated product consists of 97 % calcium ascorbate (USP/FCC), 2.9 % of hydroxypropyl methyl cellulose (E 464) and 0.1 % of tartaric acid (E 334).

The petitioner states that calcium ascorbate is an odourless, white to slightly yellow granular powder. It is soluble in water, slightly soluble in alcohol and insoluble in ether. The loss on drying is  $\leq 0.5$  % (1g, 60 °C, vacuum, 4 h). The content of arsenic is  $< 3$  mg/kg.

**Magnesium ascorbate** is described by the petitioner as an off-white to light purple powder. The solubility of magnesium ascorbate is more than 95 g/100 mL.

According to the petitioner there is no overall test for purity of magnesium ascorbate. Quantities of magnesium and ascorbic acid should meet the following specifications: magnesium 6.2 %, ascorbic acid 89.2 % (titration) and water of crystallisation 4.6 %. The content of arsenic is  $< 3$  mg/kg.

**Zinc ascorbate** is described by the petitioner as a light tan powder.

According to the petitioner there is no overall test for purity for zinc ascorbate. Quantities of zinc and ascorbic acid should meet the following specifications: zinc 15.1 %, ascorbic acid 80.7 % (titration) and water of crystallisation 4.2 %. The content of arsenic is  $< 3$  mg/kg.

The Panel notes that according to Commission Regulation (EC) No 629/2008 (EC, 2008b), 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 process of calcium-, magnesium- and zinc ascorbates has been adequately described by the petitioners.

### 2.4. Methods of analysis in food

One petitioner provided descriptions of a test method to assay ascorbate in raw materials, tablets and capsules (hard and soft) by titration, and calcium ions in raw materials, tablets and capsules (hard and soft) by Atomic Absorption Spectroscopy (AAS) and by Inductively Coupled Plasma (ICP).

Magnesium and zinc were analyzed by Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) and ascorbic acid by titration. Description of these methods has been provided by the petitioners.

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

No specific information on reaction and fate in foods were provided by the petitioners.

According to the petitioner, **calcium ascorbate** is stable for up to three years, if protected from high humidity and heat. However, no results of stability studies were included in the dossier.

According to the petitioners, all ascorbates may change colour due to oxidation without a significant decrease in the ascorbate activity. The petitioners indicated that **magnesium ascorbate** or **zinc ascorbate** are not different from other ascorbates in this respect. In addition, degradation of magnesium ascorbate or zinc ascorbate was reported to be less than 2 % after two years and less than 3 % after three years, with no formation of harmful degradation products.

### 2.6. Case of need and proposed uses

Calcium ascorbate is proposed by the petitioner as an alternative source of calcium in food supplements. The proposed use level of calcium ascorbate is up to 1500 mg/day in a food supplement providing both vitamin C and calcium. This amount corresponds to 141 mg/day of calcium and 1232 mg/day of ascorbate.

Magnesium ascorbate and zinc ascorbate are proposed by the petitioner as alternative sources of magnesium or zinc and vitamin C. According to the petitioner the particular sources allow administration of the essential trace metal and vitamin C in a single ingredient. The maximum proposed use level of magnesium ascorbate, as stated by the petitioner, is 1120.8 mg/day. This amount corresponds to 70 mg/day of magnesium and 1000 mg/day of vitamin C. The source is intended to be formulated as capsules, tablets, ampoules and powders (sachets).

The maximum proposed use level of zinc ascorbate is 66.5 mg/day. This amount corresponds to 54 mg/day of vitamin C and 10 mg/day of zinc.



## **2.7. Information on existing authorisations and evaluations**

Several calcium, magnesium and zinc salts are authorised sources of minerals for specific nutritional purposes, and calcium ascorbate is permitted as a source of vitamin C (EC, 2001).

Calcium ascorbate was evaluated by the SCF in 1987. At that time the SCF found ascorbic acid and its calcium and sodium salts acceptable for food additive use (SCF, 1989). Calcium ascorbate (E 302) is a food additive approved by the EU in all foods with no restriction other than good manufacturing practice (EC, 1995). L-ascorbic acid and its calcium, potassium and sodium salts are included in the EFSA opinion on the Tolerable Upper Intake Level of vitamin C (EFSA, 2004). Calcium L-ascorbate is accepted as a source of vitamin C in Annex II of Directive 2002/46/EC (EC, 2002). The Scientific Panel on Food Additives, Flavourings, Processing Aids and Material in Contact with Food (AFC) evaluated calcium ascorbate under the name of calcium ascorbate with a content of threonate as a source of vitamin C (EFSA, 2007).

The SCF allocated a Tolerable Upper Intake Level of 2500 mg calcium/person/day as nutrient (SCF, 2003a).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA), at its 25th meeting, included calcium ascorbate in the acceptable daily intake, not specified for ascorbic acid and its sodium and potassium salts (JECFA, 1981).

The SCF allocated a Tolerable Upper Intake Level of 250 mg magnesium/person/day as nutrient for readily dissociable magnesium salts (e.g. chloride, sulphate, aspartate, lactate), and compounds like magnesium oxide (MgO) in nutritional supplements, water, or added to food and beverages. However, this Tolerable Upper Intake Level does not include magnesium normally present in food and beverages (SCF, 2001). The Tolerable Upper Intake Level of magnesium is applicable to adults, including pregnant and lactating women, and children from four years on.

Other salts of magnesium (e.g. magnesium citrate, carbonate, chloride) or other substances containing ascorbate (e.g. calcium or potassium ascorbate) have already been approved for use in food supplements (EC, 2002). They have also been approved for use in foods for particular nutritional uses (EC, 2001).

A number of zinc salts, such as acetate, chloride, citrate, gluconate, lactate, oxide, carbonate and sulphate, have already been approved for use in the manufacture of food supplements. Other substances containing ascorbate (e.g. calcium or potassium ascorbate) have also been approved for the use in the manufacture of food supplements and are listed on Annex II of the food supplements Directive (EC, 2002). These have also been approved for the manufacture of foods for particular nutritional uses (EC, 2001).

The SCF has established Tolerable Upper Intake Levels for zinc of 25 mg/day for adults, pregnant and lactating women and children from 15 years (SCF, 2003b). For younger children, the SCF established Tolerable Upper Intake Levels of 7, 10, 13 or 18 mg/person/day for age groups of 1-3, 4-6, 7-10 or 11-14 years, respectively.

In 1982, JECFA proposed a tolerable daily intake for zinc of 0.3-1 mg/kg bw, which corresponds to 18-60 mg/day for a 60 kg person (JECFA, 1982).

The Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA) has published a report on the Tolerable Upper Intake Level of vitamin C (EFSA, 2004), where they stated: "There are insufficient data to establish a Tolerable Upper Intake Level for vitamin C. The available human data suggest that supplemental daily doses of vitamin C up to about 1

g/person/day, in addition to normal dietary intakes, are not associated with adverse gastrointestinal effects, but that acute gastrointestinal effects may occur at higher intakes (3-4 g/person/day). The absorption of vitamin C is saturated at high doses, and therefore intakes above 1 g/day would be associated with negligible increased uptake and tissue levels, but an increased risk of adverse gastrointestinal effects. The average daily intakes reported in surveys in European countries are above the recommended daily intakes, with the 95<sup>th</sup> percentile intakes from food and supplements ranging up to about 1 g/day. These dietary intakes do not represent a cause for concern” (EFSA, 2004).

The Population Reference Intake (PRI) for adults for zinc are 9.5 and 7 mg/day for males and females, respectively (range 4-12 mg/day depending on age and physiological status) (SCF, 1993), for calcium 700 mg/day (range 400-1200 mg/day depending on age and physiological status) (SCF, 2003), and for vitamin C 45 mg/day (range 25-70 mg/day depending on age and physiological status) (SCF, 1993).

## **2.8. Exposure**

### **Calcium ascorbate**

Foods particularly rich in calcium include milk (1200 mg/kg), cheese (730-12000 mg/kg) and other dairy products (except butter), green leafy vegetables (except spinach), soybean products, bread and other baked goods made from calcium fortified flour (variable levels), almonds (2400 mg/kg), brazil nuts (1700 mg/kg) and hazelnuts (1400 mg/kg). In European diets, 45 to 70 % of calcium intake is from milk and dairy products (SCF, 2003a).

According to the SCF and the UK Total Diet Study (TDS), the average and high percentile calcium intakes from food for adults in European countries vary from 683 to 944 mg/person/day and from 1308 to 1970 mg/person/day, respectively (SCF, 2003a; Ysart *et al.*, 1999).

The Panel noted that the additional exposure of 141 mg calcium/person/day, from the proposed use in food supplements, would result in an anticipated total average exposure of 824 to 1085 mg/person/day, and at the high percentile of 1449 to 2111 mg/person/day (see Table 1).

According to available data from the French food consumption survey, from the Individuelle et Nationale sur les Consommations Alimentaires (INCA2, 2009), and the French TDS (unpublished data), the average and high percentile calcium intakes from food for children vary from 804 to 809 mg/person/day and from 1338 to 1442 mg/person/day, respectively.

The Panel noted that the additional exposure of 141 mg calcium/person/day from the proposed use in food supplements would result in an anticipated total average exposure of 945 to 950 mg calcium/person/day, and at the high percentile of 1479 to 1583 mg/person/day (see Table 1).

Table 1 Summary information on calcium intake and anticipated exposure to calcium from calcium ascorbate

Nutrient: Calcium	Average intake (mg/day)	High intake (95 <sup>th</sup> or 97.5 <sup>th</sup> ) (mg/day)	References
Recommended intake adults	900-1200		SCF, 2003a
Recommended intake children	500-800 (up to 7 y) 1200-1300 (children older than 7 y and adolescents)		SCF, 2003a
Tolerable Upper Intake Level adults (including pregnant and lactating women)	2500		SCF, 2003a
Tolerable Upper Intake Level children	Insufficient data		SCF, 2003a
Intake range from food in Europe for adults	683-944	1308-1970	SCF, 2003a; Ysart <i>et al.</i> , 1999
Intake range from food in Europe for children (3-17 y)	804-809	1338-1442	French TDS; INCA2, 2009
Amount of calcium added to calcium ascorbate as indicated by the petitioner	141		Technical dossier
<b>Source : Calcium ascorbate</b>			
Total anticipated exposure to calcium from supplement and food intake <sup>1</sup> for adults.	824-1085	1449-2111	calculation by Panel
Total anticipated exposure to calcium from supplement and food intake <sup>2</sup> for children (3-17 y).	945-950	1479-1583	calculation by Panel

<sup>1</sup>Calculation based on proposed use level of 141 mg/day plus average dietary intake of 683-944 mg/day and high dietary intake of 1308-1970 mg/day for adults

<sup>2</sup>Calculation based on proposed use level of 141 mg/day plus average dietary intake of 804-809 mg/day and high dietary intake of 1338-1442 mg/day for children

According to EFSA (2004) and the French food consumption survey (INCA2, 2009), the average and the 97.5<sup>th</sup> percentile intake of vitamin C from food for adults in European countries vary from 72 to 151 mg/person/day and from 187 to 227.6 mg/person/day, respectively. The Panel noted that the additional exposure of 1232 mg/person/day, from the proposed use in food supplements, would result in an anticipated total average exposure of 1304 to 1383 mg/person/day and at the 97.5<sup>th</sup> percentile of 1419 to 1459.6 mg/person/day (see Table 4).

According to the French food consumption survey (INCA2, 2009), the average and the 97.5<sup>th</sup> percentile intake of vitamin C, from food, for children from 3 to 17 years vary from 71.1 to 84.3 mg/person/day and from 158.5 to 198.3 mg/person/day, respectively. The Panel noted that the additional exposure of 1232 mg/person/day from the proposed use in food supplements would result in an anticipated total average exposure of 1303 to 1316.3 mg/person/day, and at the 97.5<sup>th</sup> percentile of 1390.5 to 1430.3 mg/person/day (see Table 4).

### Magnesium ascorbate

Magnesium is ubiquitous in foods, but its content varies substantially. Leafy vegetables, as well as grains and nuts, generally have higher magnesium content (60-2700 mg/kg) than meats and dairy products (less than 280 mg/kg). Fats, refined sugars and pure alcohol are free of magnesium. Meat, most kinds of fish, fruit, most vegetables and dairy products contain less

than 250 mg magnesium/kg wet weight. Cacao and bitter chocolate, conches, shrimps, soybeans, butter beans and beet greens contain over 1000 mg magnesium/kg. The magnesium content of grain and grain products largely depends on processing; high concentrations (1100-1800 mg/kg) are found in whole barley, whole rye or wheat flour or brown rice (EVM, 2003; SCF, 2001).

According to the SCF, the average and the 97.5<sup>th</sup> percentile of magnesium intakes from food for adults in European countries vary from 208 to 353 mg/person/day and 350 to 628 mg/person/day, respectively (SCF, 2001). In children, the average and the 97.5<sup>th</sup> percentile of magnesium intakes from food vary from 196.3 to 227.3 mg/person/day and 297.8 to 387.4 mg/person/day, respectively (INCA2, 2009; French TDS).

The Panel noted that the exposure to magnesium from magnesium ascorbate, when used according to the recommendation of the petitioner, will be 70 mg magnesium/person/day. This would result in a total anticipated average and high percentile exposure of 278 to 423 mg/person/day and 420 to 698 mg/person/day, respectively in adults, and of 266.3 to 297.3 mg/person/day and 367.8 to 457.4 mg/person/day, respectively in children (see Table 2).

**Table 2 Summary information on magnesium intake and anticipated exposure to magnesium from magnesium ascorbate**

<b>Nutrient: Magnesium</b>	<b>Average intake (mg/day)</b>	<b>High intake (95<sup>th</sup> or 97.5<sup>th</sup>) (mg/day)</b>	<b>References</b>
Acceptable range of intake adult	150-500		SCF, 1993
Tolerable Upper Intake Level adults and children from 4 y	250*		SCF, 2001
Intake range from food in Europe for adults	208-353	350-628	SCF, 2001
Intake range from food in Europe for children (3-17 y)	196.3-227.3	297.8-387.4	French TDS; INCA2, 2009
Amount of magnesium added to magnesium ascorbate as indicated by the petitioner	70		Technical dossier
<b>Source : Magnesium ascorbate</b>			
Total anticipated exposure to magnesium from supplement and food intake <sup>1</sup> for adults.	278-423	420-698	calculation by Panel
Total anticipated exposure to magnesium from supplement and food intake <sup>2</sup> for children (3-17 y).	266.3-297.3	367.8- 457.4	calculation by Panel

\* This Tolerable Upper Intake Level is established for readily dissociable magnesium salts and compounds like magnesium oxide and does not include magnesium normally present in foods and beverages

<sup>1</sup>Calculation based on proposed use level of 70 mg/day plus average dietary intake of 208-353 mg/day and high dietary intake of 350-628 mg/day for adults

<sup>2</sup>Calculation based on proposed use level of 70 mg/day plus average dietary intake of 196.3-227.3 mg/day and high dietary intake of 297.8-387.4 mg/day for children

The Panel noted that the exposure to vitamin C, through the use of magnesium ascorbate as food supplements, may lead to an additional exposure to this vitamin of 1000 mg/person/day. This would result in an anticipated total average exposure of 1072 to 1151 mg vitamin C/person/day, and at the 97.5<sup>th</sup> percentile of 1187 to 1227.6 mg vitamin C/person/day in adults. In children, the anticipated total average exposure would vary from 1071.1 to 1084.3 mg vitamin C/person/day, and the 97.5<sup>th</sup> percentile from 1158.5 to 1198.3 mg vitamin C/person/day (see Table 4).

## Zinc ascorbate

Zinc is widely distributed in foods. Good food sources of zinc include red meat, whole wheat, raisins, unrefined cereals (high zinc content, low availability), whereas milk, fruit and vegetables are low in zinc (Sandstead and Smith Jr, 1996).

The daily average zinc intake in European adults is usually between 7.5 and 12.1 mg/person/day, and the 97.5<sup>th</sup> percentile of zinc intake varies from 15 to 20.5 mg/person/day (SCF, 2003b; Leblanc *et al*, 2005). The Panel noted that the exposure to zinc from zinc ascorbate, when used according to the recommendation of the petitioner, will be 10 mg/person/day. This would result in an anticipated total average exposure of 17.5 to 22.1 mg/person/day and at the 97.5<sup>th</sup> percentile of 25 to 30.5 mg/person/day (see Table 3).

According to the French food consumption survey, the daily average zinc intake in children vary from 7.7 to 9 mg/person/day, and the 97.5<sup>th</sup> percentile from 12.5 to 15.9 mg/person/day (INCA2, 2009). The Panel noted that the exposure to zinc from zinc ascorbate, when used according to the recommendation of the petitioner, will be 10 mg/person/day. This would result in an anticipated total average exposure of 17.7 to 19 mg/person/day and at the 97.5<sup>th</sup> percentile of 22.5 to 25.9 mg/person/day (see Table 3).

Table 3 Summary information on zinc intake and anticipated exposure to zinc from zinc ascorbate

Nutrient: Zinc	Average intake (mg/day)	High intake (95 <sup>th</sup> or 97.5 <sup>th</sup> ) (mg/day)	References
Population reference intake adults	9.5 (males) 7 (females)		SCF, 1993
Estimated average requirements	7.3 (males) 5.5 (females)		
Tolerable Upper Intake Level adults including pregnant and lactating women	25		SCF, 2003b
Tolerable Upper Intake Level children (1-3 y, 4-6 y, 7-10 y, 11-14 y, 15-17 y)	7, 10, 13, 18, 22		SCF, 2003b
Intake range from food in Europe for adults	7.5-12.1	15-20.5	SCF, 2003b Leblanc <i>et al</i> , 2005
Intake range from food in Europe for children (3-17 y)	7.7-9	12.5-15.9	French TDS; INCA2, 2009
Amount of zinc added to zinc ascorbate as indicated by the petitioner	10		Technical dossier
<b>Source : Zinc ascorbate</b>			
Total anticipated exposure to zinc from supplement and food intake <sup>1</sup> for adults.	17.5-22.1	25-30.5	calculation by Panel
Total anticipated exposure to zinc from supplement and food intake <sup>2</sup> for children (3-17 y).	17.7-19	22.5-25.9	calculation by Panel

<sup>1</sup>Calculation based on proposed use level of 10 mg/day plus average dietary intake of 7.5-12.1 mg/day and high dietary intake of 15-20.5 mg/day for adults

<sup>2</sup>Calculation based on proposed use level of 10 mg/day plus average dietary intake of 7.7-9 mg/day and high dietary intake of 12.5-15.9 mg/day for children

The Panel noted that the exposure to vitamin C, through use of zinc ascorbate as a supplement,

supplement, may lead to an additional exposure to this vitamin of 54 mg/person/day, thus resulting to an average anticipated exposure of 126 to 205 mg/person/day and a high percentile exposure of 241 to 281.6 mg/person/day in adults (see Table 4). In children, the average and high percentile exposure will vary from 266.3 to 297.3 mg/person/day and from 367.8 to 457.4 mg/person/day, respectively (see Table 4).

**Table 4 Summary information on vitamin C intake and anticipated exposure to vitamin C from calcium ascorbate, magnesium ascorbate and zinc ascorbate**

<b>Nutrient: Vitamin C</b>	<b>Average intake (mg/day)</b>	<b>High intake (95<sup>th</sup> or 97.5<sup>th</sup>) (mg/day)</b>	<b>References</b>
Population reference intake adults	45		SCF, 1993
Tolerable Upper Intake Level adults and children	Insufficient data Acute gastrointestinal intolerance may occur at 3-4 g/day		EFSA, 2004
Intake range from food in Europe for adults	72-151	187-227.6	EFSA, 2004 French TDS INCA2, 2009
Intake range from food in Europe for children (3-17 y)	71.1-84.3	158.5-198.3	French TDS INCA2, 2009
<b>Source: Calcium ascorbate</b>			
Amount of vitamin C added to calcium ascorbate as indicated by the petitioner	1232		Technical dossier
Total anticipated exposure to vitamin C from supplement and food intake <sup>1</sup> for adults.	1304-1383	1419-1459.6	calculation by Panel
Total anticipated exposure to vitamin C from supplement and food intake <sup>2</sup> for children (3-17 y).	1303.1-1316.3	1390.5-1430.3	calculation by Panel
<b>Source: Magnesium ascorbate</b>			
Amount of vitamin C added to magnesium ascorbate as indicated by the petitioner	1000		Technical dossier
Total anticipated exposure to vitamin C from supplement and food intake <sup>3</sup> for adults.	1072-1151	1187-1227.6	calculation by Panel
Total anticipated exposure to vitamin C from supplement and food intake <sup>4</sup> for children (3-17 y).	1071.1-1084.3	1158.5-1198.3	calculation by Panel
<b>Source: Zinc ascorbate</b>			
Amount of vitamin C added to zinc ascorbate as indicated by the petitioner	54		Technical dossier
Total anticipated exposure to vitamin C from supplement and food intake <sup>5</sup> for adults.	126-205	241-281.6	calculation by Panel
Total anticipated exposure to vitamin C from supplement and food intake <sup>6</sup> for children (3-17 y).	125.1-138.3	212.5-252.3	calculation by Panel

<sup>1</sup>Calculation based on proposed use level of 1232 mg/day plus average dietary intake of 72-151mg/day and high dietary intake of 187-227.6 mg/day for adults.

<sup>2</sup>Calculation based on proposed use level of 1232 mg/day plus average dietary intake of 71.1-84.3 mg/day and high dietary intake of 158.5-198.3 mg/day for children.

<sup>3</sup>Calculation based on proposed use level of 1000 mg/day plus average dietary intake of 72-151 mg/day and high dietary intake of 187-227.6 mg/day for adults.

<sup>4</sup>Calculation based on proposed use level of 1000 mg/day plus average dietary intake of 71.1-84.3 mg/day and high dietary intake of 158.5-198.3 mg/day for children.

<sup>\*5</sup>Calculation based on proposed use level of 54 mg/day plus average dietary intake of 72-151mg/day and high dietary intake of 187-227.6 mg/day for adults.

<sup>6</sup>Calculation based on proposed use level of 54 mg/day plus average dietary intake of 71.1-84.3 mg/day and high dietary intake of 158.5-198.3 mg/day for children.

### 3. Biological and toxicological data

#### 3.1. Bioavailability and absorption

##### Bioavailability of calcium from calcium ascorbate

The petitioner did not provide any data on bioavailability of calcium from the source or studies comparing the bioavailability of calcium from this and other sources.

Calcium ascorbate dissociates in the acid conditions of the stomach. Once dissociated the calcium and ascorbic acid behave in the same way as the ions disassociated from other sources in the gastrointestinal contents. The absorption of calcium and ascorbic acid has been described both by the SCF (SCF, 2003a) and EFSA (EFSA, 2004). Based on the predicted dissociation of calcium ascorbate, the bioavailability of calcium and ascorbic acid from calcium ascorbate would be expected to be similar to that from other dissociable forms of calcium and ascorbic acid in the gastrointestinal tract.

##### Bioavailability of magnesium and vitamin C from magnesium ascorbate

The petitioner did not present any human or animal studies on bioavailability of magnesium or vitamin C from the source of magnesium ascorbate, or studies comparing the bioavailability of magnesium and vitamin C from this and other sources.

A single *in vitro* study of intestinal absorption of magnesium from magnesium ascorbate and other sources was presented by the petitioner. The *in vitro* model system consisted of the isolated section of rat small intestine. The sources of magnesium ion ( $Mg^{2+}$ ) were magnesium chloride, magnesium sulphate, magnesium acetate, magnesium lactate, magnesium hydrocitrate and magnesium ascorbate. Magnesium ions from magnesium ascorbate were absorbed after the first 15 minutes to the highest extent of all salts, but after 120 minutes their absorption was the smallest of all. The availability of magnesium hydrocitrate was almost 1.5 times higher than that of magnesium ascorbate (Ryszka *et al.*, 1992).

It can be assumed that magnesium ascorbate will dissociate in the acid conditions of the stomach. Based on the predicted dissociation of magnesium ascorbate, the bioavailability of magnesium and ascorbic acid from magnesium ascorbate would be expected to be similar to other dissociable forms of magnesium and ascorbic acid in the gastrointestinal tract.

##### Bioavailability of zinc and vitamin C from zinc ascorbate

The petitioner did not provide any data on the bioavailability of zinc or ascorbate from the source or studies comparing the bioavailability of zinc or ascorbate from this and other sources.

According to the petitioner, zinc ascorbate readily dissociates in the acid conditions of the stomach. Based on the predicted dissociation of zinc ascorbate, the bioavailability of zinc and ascorbic acid from zinc ascorbate would be expected to be similar to other dissociable forms of zinc and ascorbic acid in the gastrointestinal tract.

### **3.2. Metabolic fate of the sources and biological distribution of calcium, magnesium and zinc ascorbates**

The petitioners did not provide any details on the metabolic fate of calcium, magnesium and zinc ascorbates.

Upon ingestion ascorbate salts dissociate in the stomach. The absorption and metabolic fate of calcium, magnesium and zinc cations has been described previously by the SCF (SCF 2001; SCF 2003a,b). The metabolism of vitamin C has been described by EFSA (EFSA, 2004).

### **3.3. Toxicological data**

No data on toxicological aspects of the calcium-, magnesium- and zinc ascorbate were submitted.

## **4. Discussion**

Based on the considerations of dissociation in the gastrointestinal tract, the Panel considers that the bioavailability of calcium, magnesium, zinc and ascorbic acid from calcium ascorbate, magnesium ascorbate and zinc ascorbate is expected to be comparable to their bioavailability from other dissociable salts which are permitted sources of these nutrients in food supplements.

Given the previous evaluation of calcium ascorbate as a food additive (E 302) and as a food supplement source of vitamin C, further toxicological evaluation of calcium ascorbate is not needed for the present opinion.

Given the previous evaluations of magnesium and zinc to establish the Tolerable Upper Intake Level for these minerals and the previous evaluation of L-ascorbic acid as a food supplement source of vitamin C, toxicological evaluations of magnesium ascorbate and zinc ascorbate are not needed for the present opinion.

The Panel notes that the total exposure to calcium, from food and through use of calcium ascorbate as a food supplement, at the use and use levels proposed by the petitioner (up to 1500 mg calcium ascorbate/person/day, which equates up to 141 mg of calcium and up to 1232 mg vitamin C), will not exceed the Tolerable Upper Intake Level of 2500 mg/person/day for calcium established for adults by the SCF.

The Panel notes the following:

- The exposure to vitamin C, through the use of calcium ascorbate as a food supplement, may lead to an additional exposure to this vitamin of 1232 mg/person/day. The Panel notes that the NDA Panel concluded that supplemental daily doses of this magnitude, in addition to normal dietary intakes, were not associated with adverse gastrointestinal



associated with adverse gastrointestinal effects, but that acute gastrointestinal effects may occur at higher intakes (3-4 g/day). The Panel anticipates that the exposure to vitamin C of users of calcium ascorbate supplements, at the use and use levels proposed by the petitioner, will be below the amounts which may give rise to acute gastrointestinal symptoms.

- The exposure to magnesium, through the use of magnesium ascorbate as a food supplement at the use and use levels proposed by the petitioner will be 70 mg magnesium/person/day. This exposure will not exceed the Tolerable Upper Intake Level of 250 mg/person/day for readily dissociable magnesium salts, taken in addition to magnesium present in normal food and beverages (based on a NOAEL for mild transient laxative effect in humans, and which holds for adults, including pregnant and lactating women and children from 4 years on) established by the SCF.
- The use of magnesium ascorbate in food supplements may lead to an additional exposure to vitamin C of 1000 mg/person/day. Supplemental daily doses of this magnitude, in addition to normal dietary intakes, are not associated with adverse gastrointestinal effects, but these acute effects may occur at intakes of 3-4 g vitamin C/person/day (EFSA, 2004).
- The anticipated total mean exposure to zinc from food and food supplements of users of zinc ascorbate at the use levels proposed by the petitioner (up to 66.5 mg/person/day which equates to 10 mg of zinc and 54 mg vitamin C) will not exceed the Tolerable Intake Upper Level of 25 mg/person/day for adults, pregnant and lactating women, and children older than 15 years (SCF, 2003b). For children less than 15 years old, the anticipated total mean exposure may exceed the respective Tolerable Upper Intake Levels of 7, 10, 13 or 18 mg/person/day for age groups of 1-3, 4-6, 7-10 or 11-14 years, respectively. At the 97.5<sup>th</sup> percentile of total zinc intake, the Tolerable Upper Intake Level for zinc will be exceeded for adults and children of all age groups.
- The use of zinc ascorbate in food supplements may lead to an additional exposure to the vitamin C of 54 mg/person/day, which is much lower than the doses associated with adverse acute gastrointestinal effects (3-4 g/person/day).
- The exposure to vitamin C from all the three sources, at the use and use levels proposed by the petitioners, will be 2283 mg/person/day. This amount may be associated with an increased risk of adverse gastrointestinal effects. The acute gastrointestinal effects may occur at higher intakes (3-4 g/person/day).

## 5. Conclusions

The present opinion deals only with the safety of calcium ascorbate as a particular source of calcium, magnesium ascorbate as a particular source of magnesium and vitamin C, zinc ascorbate as a particular source of zinc and vitamin C, and with the bioavailability of the nutrient cations from these sources and the vitamin C bioavailability from magnesium ascorbate and zinc ascorbate.

The Panel concludes that the bioavailability of calcium, magnesium or zinc from the sources of calcium ascorbate, magnesium ascorbate or zinc ascorbate, and of vitamin C from the sources of magnesium ascorbate or zinc ascorbate is not expected to differ from that of already

already permitted sources of calcium, magnesium, zinc and vitamin C for food supplements.

The Panel concludes that the use of calcium ascorbate as a source of calcium, and of magnesium ascorbate as a source of magnesium and vitamin C in food supplements at the use levels proposed by the petitioners is not of safety concern.

For zinc ascorbate as a source of zinc at the use and the use levels proposed by the petitioner the anticipated total mean exposure to zinc from food and food supplements is of no safety concern for adults and pregnant and lactating woman and children of 15 years of age or more. However for children less than 15 years old, the anticipated total mean exposure may exceed the respective Tolerable Upper Intake Levels. At the 97.5<sup>th</sup> percentile of the total zinc intake the upper level for zinc will be exceeded for adults and children of all age groups. The Panel concludes that the use of zinc ascorbate as a source of zinc and vitamin C in food supplements is not of safety concern. However the Panel is concerned that when the dietary intake is also taken into consideration, in the case of food supplements providing 66.5 mg zinc ascorbate or above, the Tolerable Upper Intake Level for zinc established by the SCF will be exceeded.

## DOCUMENTATION PROVIDED TO EFSA

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2. Dossier on Zinc ascorbate. May 2005. Submitted by Natuur- & gezondheids Producten, The Netherlands.
3. Dossier on Calcium ascorbate Proposed for Addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. July 2005. Submitted by Solgar Vitamin and Herb. England.

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**GLOSSARY / ABBREVIATIONS**

AAS	Atomic Absorption Spectroscopy
AFC	Scientific Panel on Food Additives, Flavourings, Processing Aids and Material in Contact with Food
ANS	Scientific Panel on Food Additives and Nutrient Sources added to Food
CAS	Chemical Abstract Service
EC	European Commission
EFSA	European Food Safety Authority
FCC	Food Chemical Codex
ICP	Inductively Coupled Plasma
ICP-OES	Inductively Coupled Plasma Optical Emission Spectrometry
INCA	Individuelle et Nationale sur les Consommations Alimentaires
JECFA	Joint FAO/WHO Expert Committee on Food Additives
NDA	Scientific Panel on Dietetic Products, Nutrition and Allergies
NOAEL	No observable adverse effect level
PRI	Population Reference Intake
SCF	Scientific Committee on Food
TDS	Total Diet Study
USP	United States Pharmacopoeia