SCIENTIFIC OPINION

Calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate added for nutritional purposes to food supplements

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


Adopted on 17 December 2008

PANEL MEMBERS


SUMMARY

Following a request from the Commission, the Panel on Food Additives and Nutrient Sources added to Food (ANS) has been asked to deliver a scientific opinion on calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate, added for nutritional purposes to food supplements.

The present opinion deals only with the safety of specific methionates as sources for respectively calcium, magnesium and zinc added for nutritional purposes to food supplements. The safety of calcium, magnesium and zinc is outside the remit of the ANS Panel.

The Panel noted that for calcium L-methionate and magnesium L-methionate no specific data demonstrating the bioavailability of the cations calcium and magnesium from these sources have been provided. However data from studies on the bioavailability of related sources of calcium and magnesium (i.e. salts of organic acids and amino acids) have shown the cations

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1 For citation purposes: Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food on a request from the Commission on calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate as sources for calcium, magnesium and zinc added for nutritional purposes to food supplements. The EFSA Journal (2008) 924, 1-26.
Calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate added for nutritional purposes to food supplements

to be bioavailable. Calcium L-methionate and magnesium L-methionate are expected to dissociate before being readily absorbed in the intestine. The bioavailability of zinc from zinc mono-L-methionine sulphate has been demonstrated based on studies in humans, animals and supplementation studies with livestock. Therefore, the Panel concludes that the bioavailability of calcium, magnesium and zinc from calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate respectively is expected to be similar to that of other comparable sources of these nutrients.

For calcium L-methionate, the highest reported calcium content in single and in the most common multiple nutrient supplements on the market is 1200 mg. If all the calcium in food supplements were to be provided by the addition of calcium L-methionate, this would lead to a potential dietary exposure of about 9 g methionine/day, corresponding to 149 mg methionine/kg bw/day for a 60 kg person. The Panel considers an exposure to 149 mg methionine/kg bw/day from calcium L-methionate to be a conservative estimate.

For magnesium L-methionate, if all the magnesium in food supplements were to be provided by the addition of this magnesium source at the Tolerable Upper Intake Level (UL) of 250 mg magnesium/day, the equivalent exposure to methionine would be about 3 g/day, corresponding to 51 mg methionine/kg bw/day for a 60 kg person. The Panel considers an exposure to 51 mg methionine/kg bw/day from magnesium L-methionate to be a conservative estimate.

For zinc mono-L-methionine sulphate, if all the zinc in food supplements were to be provided by the addition of zinc mono-L-methionine sulphate (CAS No 56329-42-1) at the upper level of 25 mg zinc per day, the potential exposure to methionine would be about 57 mg methionine/day, corresponding to about 0.95 mg methionine/kg bw/day for a 60 kg person. The Panel considers an exposure to 0.95 mg methionine/kg bw/day from zinc mono-L-methionine sulphate to be a conservative estimate.

Exposure to zinc mono-L-methionine sulphate also results in an exposure to sulphate. Under the same assumption as above the exposure to sulphate from the addition of zinc mono-L-methionine sulphate would be 73 mg sulphate/day, equivalent to 1.2 mg sulphate/kg bw/day for a 60 kg person. Based on a former evaluation by the Panel on the safety of sulphate from calcium sulphate, the Panel is of the opinion that an exposure to 1.2 mg sulphate does not raise a safety concern.

The Panel further notes that if in a multivitamin supplement all calcium, magnesium and zinc at the above listed levels were to be provided as the methionate form this would result in a methionine intake of (149 mg/kg bw/day + 51 mg/kg bw/day + 0.95 mg/kg bw/day) about 200 mg methionine/kg bw/day or 12 g per day for a 60 kg person.

The Panel considered the safety of methionine resulting from the use of the different supplements under consideration. A dose of methionine of 100 mg/kg bw (i.e. 6 g for a 60 kg person) resulted in an acute increase in plasma homocysteine. A dose of 1 g/kg bw (i.e. 60 g for a 60 kg person) given in error resulted in death while methionine intakes 5 times higher than normal (i.e. intakes approximately 12.5 g methionine/day; normal intakes being estimated at about 2.5 g methionine/day) resulted in elevated homocysteine levels. However, longer-term studies in adults indicated no adverse effects of moderate fluctuations in dietary methionine intake. In line with the Scientific Committee for Food (SCF), 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 the use of methionine sources at these levels, together giving rise to a methionine intake of 12 g per day for a 60 kg person, could be of safety concern.
As already indicated, if calcium was to be supplied at the highest level (1200 mg) as calcium L-methionate, the Panel calculated that the potential exposure to methionine would be about 9 g methionine/day for an adult. The Panel notes that this would be an additional exposure above the normal intake of methionine from the diet (i.e. about 2.5 g/day) resulting in a total intake of approximately 11.5 g methionine/day. The Panel has no data that demonstrate that such a level of methionine intake would be safe.

Similarly, for magnesium L-methionate, if magnesium was supplied at the UL (250 mg magnesium/day) the Panel calculated an exposure to methionine of about 3 g methionine/day resulting in a total methionine intake (supplemental + dietary) of approximately 5.5 g/day. The Panel has no data to prove that this would be a safe intake level for methionine.

The Panel further calculated that in the case of zinc mono-L-methionine sulphate, if all the zinc in food supplements were to be provided by zinc mono-L-methionine sulphate (CAS No 56329-42-1) at the upper level of 25 mg zinc per day the potential exposure to methionine would be 57.2 mg methionine/day. The Panel considers this level of methionine to be of no safety concern.

Finally, the Panel notes that the SCF evaluated the general safety of L-amino-acids and considered their use acceptable provided that their addition to food does not give rise to a nutritional imbalance of the amino acids.

In the absence of data that demonstrate the safety of the potential total exposure to about 11.5 g methionine/day resulting from intakes from both calcium L-methionate supplements and from the diet, or to about 5.5 g methionine/day from both magnesium L-methionate supplements and from the diet, the Panel concludes that the proposed use levels of calcium L-methionate and magnesium L-methionate as sources for calcium and magnesium at the proposed levels of use could be of safety concern.

Although the safety of zinc itself, in terms of the amounts that may be safely consumed, is outside its remit, the Panel wishes to indicate that, at the 97.5th percentile the dietary zinc intake from total food only is already close to the UL established by the SCF. The intake of zinc from food supplements and/or fortified food in addition to the normal dietary zinc intake could cause the UL to be exceeded, especially for consumers at high percentiles.

The Panel further concludes that in the case of zinc mono-L-methionine sulphate the potential exposure to methionine and sulphate is negligible compared to the normal dietary intake of these compounds and that the use of zinc mono-L-methionine sulphate at the proposed level of use as a source of zinc is not of safety concern.

Key words:
Calcium L-methionate, CAS No: 7786-71-2; Magnesium L-methionate, CAS No: 106207-65-2; Zinc mono-L-methionine sulphate, Hydrogen (CL-methioninato-N,O,S)(sulphato(2-)-O)zincate(1-) CAS No 56329-42-1).
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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 calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate added for nutritional purposes to food supplements. The relevant Community legislative measure is:


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 L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate added for nutritional purposes to food supplements.

ACKNOWLEDGEMENTS

ASSESSMENT

1. Introduction

The present opinion deals only with the safety of calcium L-methionate, magnesium L-methionate and of zinc mono-L-methionine sulphate as sources of calcium, magnesium and zinc and with the bioavailability of the nutrient cations from these sources. The safety of magnesium, calcium and zinc, in terms of the amounts that may be consumed, is outside the remit of this Panel.

This opinion is based on information provided by two petitioners.

2. Technical data

2.1. Chemistry and specifications

Calcium L-methionate and magnesium L-methionate are complexes formed by bivalent metal (M^{2+}) linked to two molecules of methionine.

![General structural formula](image)

Figure 1. **General structural formula** (‘M’, represents the ions calcium(II) or magnesium(II)).

*Calcium L-methionate*

Calcium L-methionate has the empirical formula Ca(C_5H_{10}NO_2S)_2, CAS No 7786-71-2 and a molecular weight of 336.5 g/mol. It is described as a white crystalline powder, slightly soluble in water.

The petitioner indicates that the purity of the source is not less than 98.0%. The Panel calculated the calcium content in the source to be not less than 122 mg/g.

Specifications for calcium L-methionate as provided by the petitioner are given in Table 1.

| Chemical specifications proposed for calcium L-methionate |
|-----------------|----------------|----------------|----------------|----------------|
| **Ca(C_5H_{10}NO_2S)_2** | **Assay** | **Arsenic** | **Lead** | **Mercury** |
| | **98 %** | **< 3 mg/kg** | **< 5 mg/kg** | **< 1 mg/kg** | **Positive test for calcium** |

The EFSA Journal (2008) 924, 6-26
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 3.0 mg/kg and 0.1 mg/kg and 1 mg/kg respectively (EC, 2008).

The petitioner states that the chemical identity of the source is checked by infrared (IR) spectrometry on a finely ground sample of calcium L-methionate incorporated in a Nujol mull or in a KBr disk. The petitioner provides an IR spectrum used as a ‘fingerprint’ to confirm the identity of the source.

**Magnesium L-methionate**

Magnesium L-methionate has the empirical formula Mg(C₅H₁₀NO₂S)₂, CAS No: 106207-65-2 and a molecular weight of 320.74 g/mol. It is described as a white crystalline powder, soluble in water.

The petitioner indicates that the purity of the source is not less than 98.0% based on the anhydrous form. The Panel calculated the magnesium content in the source to be not less than 77 mg/g based on the anhydrous form.

Specifications for magnesium L-methionate as provided by the petitioner are presented in Table 2.

**Table 2. Chemical specifications proposed for magnesium L-methionate**

<table>
<thead>
<tr>
<th>Assay</th>
<th>Arsenic</th>
<th>Lead</th>
<th>Mercury</th>
<th>Identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mg(C₅H₁₀NO₂S)₂</td>
<td>98 %</td>
<td>&lt; 3 mg/kg</td>
<td>&lt; 5 mg/kg</td>
<td>&lt; 1 mg/kg</td>
</tr>
</tbody>
</table>

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 3.0 mg/kg, 0.1 mg/kg and 1 mg/kg respectively (EC, 2008).

The petitioner states that the chemical identity of the source is checked by IR spectrometry using a finely ground sample of magnesium L-methionate incorporated in a Nujol mull or in a KBr disk. The petitioner provides an IR spectrum used as a ‘fingerprint’ to confirm the identity of the source.

**Zinc(II) mono-L-methionine sulphate**

Zinc(II) mono-L-methionine sulphate [synonyms: Hydrogen (CL-methioninato-N,O,S)(sulphato(2-)-O)zincate(1-), Zinc methionine bisulfate, Zinc methionine, Zinc-L-methionine, Zinc monomethionine], CAS Registry number: 56329-42-1, has the empirical formula [C₅H₁₀NO₂S Zn]⁺ HSO₄⁻ and a molecular weight of 310.665 g/mol.
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Figure 2. Structural formula of zinc(II) mono-L-methionine sulphate as provided by the petitioner (zinc presented as Zn$^{+2}$).

The petitioner provided the results of the analysis of zinc in four different batches demonstrating that the zinc content in the source may vary between 207 and 214 mg/g. The petitioner states that the zinc content in the source is never less than 200 mg/g.

The formulation with zinc mono-L-methionine sulphate as main ingredient is described as a fine white, non fibrous powder. The formulation contains: zinc 21%, methionine 42%, sulphate 35%, water 2% and silica and flavouring accounting for 0.4% and 0.15% respectively. The solubility is 2 g per 100 mL water (50°C). The pH of a 1% solution of the product is within the range 4.0 – 5.0.

Specifications for zinc mono-L-methionine sulphate as provided by the petitioner are given in Table 3.

Table 3. Chemical specifications proposed for zinc mono-L-methionine sulphate

<table>
<thead>
<tr>
<th></th>
<th>Zn</th>
<th>Methionine</th>
<th>Arsenic</th>
<th>Cadmium</th>
<th>Lead</th>
<th>Mercury</th>
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<tr>
<td>(C$<em>{10}$H$</em>{17}$NO$_2$S Zn)$^{+}$</td>
<td>No &lt; 200 mg/g</td>
<td>420 ± 40 mg/g</td>
<td>&lt; 3 mg/kg</td>
<td>&lt; 1 mg/kg</td>
<td>&lt; 5 mg/kg</td>
<td>&lt; 0.3 mg/kg</td>
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<tr>
<td>HSO$_4^{-}$</td>
<td></td>
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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 3.0 mg/kg, 0.1 mg/kg and 1 mg/kg respectively (EC, 2008).

The finished product is evaluated using HPLC (for determination of methionine) and Inductively Coupled Plasma (ICP) (for zinc). Methodologies used are described by the petitioner in the application dossier. No impurities other than heavy metals have been detected.

2.2. Manufacturing process

Calcium L-methionate is stated by the petitioner to be manufactured synthetically by the reaction of a soluble calcium salt with L-methionine. Magnesium L-methionate is stated by the petitioner to be manufactured synthetically from magnesium sulphate and L-methionine.

As regards zinc mono-L-methionine sulphate, the manufacturing process of the formulation containing zinc L-methionine is described by the petitioner as a reaction between zinc sulphate and L-methionine.
No further details on the manufacturing processes are provided by the petitioners.

2.3. Methods of analysis in food

The petitioners provide limited information on the methods for the analysis of the sources in foods.

For calcium and magnesium the petitioner only indicates that after an appropriate extraction and preparation the content of calcium, magnesium and zinc can be assayed by Inductively Coupled Plasma (ICP) or Atomic Emission Spectrometry.

For zinc mono-L-methionine sulphate the petitioner provides a description of the HPLC method to assay the content of methionine in the finished products and for its determination in food supplements.

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

Calcium L-methionate and magnesium L-methionate are stated by the petitioner to be stable in food supplements but no data have been provided.

Zinc mono-L-methionine sulphate. The petitioner indicates that under normal conditions, at room temperature and out of direct sunlight, no degradation of the formulation containing zinc L-methionine is anticipated. Except for when the pH exceeds normal physiological levels and when exposed to excessive heat, no reactions or reaction products are anticipated.

2.5. Case of need and Proposed Uses

One petitioner states that calcium L-methionate and magnesium L-methionate will be used by food supplement formulators as a nutrient in food supplements, in the form of tablets, caplets, capsules, chewable tablets, effervescent powders and liquids, to provide a source of calcium and magnesium. It is further stated that the method of incorporation will be determined by the individual formulators.

The petitioner indicates that the quantity of calcium L-methionate and magnesium L-methionate to be added to food supplements for adults will be determined by individual formulators but it is normally the quantity necessary to supply 800 mg calcium/day and 250 mg magnesium/day respectively.

The petitioner for zinc mono-L-methionine sulphate indicates that the source is intended for use in foods and dietary supplements as a stand-alone ingredient or in multi-ingredient formulas, as a powder, in tablets, two-piece hard gelatine capsules or soft gelatine capsules. This petitioner indicates that the intake recommendations would be consistent with ‘Estimated Safe and Adequate Daily Dietary Intakes’ (ESADDI) and ‘Recommended Daily Intake’ (RDI) levels (COMA, 1991; SCF, 1993).
2.6. Exposure

2.6.1. Methionine

Methionine, an essential amino acid, is found in different food sources such as beans (250 to 350 mg/100 g edible portion), eggs (whole, 380 mg/100 g), fish (various, ~530 mg/100 g), poultry (chicken meat, ~520 mg/100 g), meat (beef, 430 mg/100 g), milk (75 mg/100 g), soybeans (547 mg/100 g), spinach (53 mg/100 g), garlic (76 mg/100 g) (USDA, 2008).

The Institute of Medicine (IOM) reported that based on 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 34,000 people) the mean intake of methionine ranged from 1.13 g/day (children 1-3 years) to 2.54 g/day (males 19-30 years). At the 95th percentile methionine intakes ranged from 2.00 g/d (children 1-3 years) to 3.55 g/day (males 19-30 years) (IOM, 2002). Assuming a standard body weight of 15 kg for children aged 1-3 years and 60 kg for an adult, average and high level intakes would correspond to 75 mg/kg bw/day and 133 mg/kg bw/day respectively in young children, and 42 mg/kg bw/day and 59 mg/kg bw/day respectively in adults.

The Panel notes that the nutritional requirement for methionine is 10 mg/kg bw/day or 600 mg/day for a 60 kg person (FAO/WHO/UNO, 2002).

2.6.2. Exposure to calcium L-methionate

Foods that are 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).

According to Scientific Committee for Food (SCF) (2003a) the average and 97.5th percentile calcium intakes from food and supplements in European countries varies from 683 to 949 mg/person/day and from 1317 to 1970 mg/person/day, respectively.

The petitioners indicate that the anticipated exposure to calcium in food supplements varies according to self-selection of products containing multivitamins and multiminerals or as more specific combinations providing calcium. As indicated above, typical levels of calcium included in food supplements will be up to 800 mg/day for adults. Such a supplementation would give a calculated exposure to methionine of about 5940 mg/day, corresponding to 99 mg methionine/kg bw/day for a person with a standard body weight of 60 kg.

The Panel noted that according to the UK Expert Committee on Vitamins and Minerals (EVM) (2003) the highest reported calcium content in single and the most common multiple nutrient supplements on the market is 1200 mg. If all the calcium in food supplements were to be provided by the addition of calcium L-methionate, this would lead to a potential dietary exposure to about 8935 mg methionine/day, corresponding to 149 mg methionine/kg bw for a 60 kg person. Based on this information the Panel considers an exposure to 149 mg methionine/kg bw/day from calcium L-methionate to be a conservative estimate.
2.6.3. Exposure to magnesium L-methionate

Magnesium is ubiquitous in foods, but its content varies substantially. Leafy vegetables, as well as grains and nuts, generally have a higher magnesium content (60-2700 mg/kg) than meats and dairy products (less than 280 mg/kg). Fats, refined sugars and pure alcohol do not contain 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, wheat flour and brown rice (EVM, 2003), (SCF, 2001).

According to the SCF (2001) the average and 97.5 percentile magnesium intakes from food and supplements in European countries vary from 208 to 353 mg/person/day and 350 to 618 mg/person/day, respectively.

The petitioners indicate that magnesium salts in general are used in food supplements at levels providing up to 750 mg/day (EVM, 2003). However, the petitioners stress that the food supplement products containing magnesium L-methionate would only normally supply up to 250 mg/day magnesium. In the case of magnesium L-methionate, if all the magnesium in food supplements were to be provided by the addition of this magnesium source at the Tolerable Upper Intake Level (UL) of 250 mg magnesium/day (SCF, 2001), the equivalent exposure to methionine would be 3069 mg/day corresponding to 51 mg methionine/kg bw/day for a 60 kg person. Based on this upper limit for supplemental magnesium, the Panel considers an exposure to 51 mg methionine/kg bw/day from magnesium L-methionate to be a conservative estimate.

The Panel noted that according to the EVM (2003) the highest magnesium content in single nutrient supplements on the market is 750 mg and in multiple nutrient supplements is 500 mg. In case the upper limit of 250 mg supplemental magnesium is exceeded, the exposure may amount up to 9180 mg magnesium/day, equivalent to 153 mg methionine/kg bw/day for a 60 kg person.

2.6.4. Exposure to Zinc mono-L-methionine sulphate

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

According to the SCF (2003b) mean intakes of zinc in adults in Europe ranged from 7.5 mg/day to 12.1 mg/day. At the 97.5th percentile the highest intake values were observed in Ireland (23.5 and 22.1 mg/day in men and women, respectively, including supplement use), in Austria (21.9 mg/day, supplement use not defined) and in German men (20.5 mg/day, supplements not included).

The Panel noted that according to the EVM (2003), the highest zinc content in single nutrient supplements on the market is 50 mg and in multiple nutrient 20 mg. The Panel noted that the SCF established for zinc from all sources an UL of 25 mg/day (SCF, 2003b). In case of zinc mono-L-methionine sulphate, if all the zinc in food supplements were to be provided by the addition of zinc mono-L-methionine sulphate (CAS No 56329-42-1) at the upper level of 25 mg zinc per day, the potential exposure would be 57.2 methionine mg/day and to 36.4 mg sulphate/day, corresponding to about 0.95 mg methionine/kg bw/day and to 0.61 mg sulphate.
Calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate added for nutritional purposes to food supplements

/ kg bw/day for a 60 kg person. Based on this upper level for zinc, the Panel considers an exposure to 0.95 mg methionine/kg bw/day to be a conservative estimate.

The Panel also noted that the UL for zinc is related to total zinc intake. The EVM established a ‘Safe Upper Level’ (SUL) of 25 mg/day for supplemental zinc (EVM, 2003) whereas the IOM tolerable upper intake level of 40 mg/day applied to dietary and supplemental zinc intake (IOM, 2001). The Panel noted that, although the safety of zinc itself, in terms of amounts that may be consumed, is outside the remit of this Panel, at the 97.5th percentile the dietary zinc intake from total food only is already close to the UL as established by the SCF. Most use levels in food supplements (30 mg zinc per capsule at the mean with a range of 15-50 mg) exceed the population reference intake (PRI) and the UL. Intake of zinc from food supplements and/or fortified food in addition to the normal zinc intake could cause the UL to be exceeded, especially for consumers at high percentiles.

The Panel noted that according to the EVM (2003) the highest zinc content in nutrient supplements on the market is 50 mg which exceeds the UL established by the SCF by 2-fold. In this case the exposure may amount up to approximately 114 mg methionine/day and to 73 mg sulphate/day, equivalent to 1.9 mg methionine/kg bw/day and to 1.2 mg sulphate/kg bw/day for a 60 kg person.

If in a multivitamin supplement all calcium, magnesium and zinc at the above listed levels (conservative estimates) were to be provided by the methionate form this would result in a methionine intake of (149 mg/kg + 51 mg/kg + 0.95 mg/kg) about 200 mg methionine/kg bw/day or 12 g/day.

2.7. Information on existing authorisations and evaluations

In 1993 the SCF established the population reference intakes (PRI) for calcium. More recent reports (IOM, 1997; D-A-CH, 2000; AFSSA, 2001) include the attainment of peak bone mass during childhood, adolescence and young adulthood in their calculations. The adequate intakes (AI) and recommended daily intakes (RDI) thus derived are generally higher than the PRI. They are between 500 and 800 mg calcium per day for children up to the age of 7 years, 1200 to 1300 mg calcium per day for older children and adolescents and 900 to 1200 mg calcium per day for adults. Pregnant and lactating women below the age of 18 years should receive between 1200 and 1300 mg calcium per day (SCF, 2003a).

For magnesium the SCF (1993) determined an Acceptable Range of Intake for Adults of 150-500 mg/day. In the UK, Reference Nutrient Intake (RNI) values are 300 mg/day for adult males and 270 mg/day for adult females (whereas in the US the recommended intake is 400-420 mg/day for adult males and 300-320 mg/day for adult females, depending on age (IOM, 1997).

The European Population Reference Intake (PRI) and the UK Reference Nutrient Intake (RNI) for zinc (SCF, 1993; COMA, 1991) for adult males and females are 9.5 mg/day and 7.0 mg/day, respectively. In the US, new guidelines recommend daily zinc intakes of 11 mg/day for adult men and 8 mg/day for adult women (IOM, 2001).

For calcium, magnesium and zinc, the following UL’s have been established by the SCF: 2500 mg calcium/day for adults from all sources (SCF, 2003a), 250 mg magnesium/day for readily dissociable magnesium salts and compounds like magnesium oxide, not including magnesium normally present in foods and beverages for adults and children from 4 years on (SCF, 2001), and 25 mg zinc/day for adults from all sources (SCF, 2003b).
Calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate added for nutritional purposes to food supplements

The Panel noted that supplements containing more than 250 mg magnesium exceed the UL established by the SCF (2001). The EVM (2003) could not establish a SUL for magnesium but provided a guidance level of 400 mg magnesium/day for supplemental use. The IOM (2001) established tolerable upper level of 350 mg for supplemental use for adults and children from 8 years and over.

The sodium, potassium, calcium and magnesium salts of L-methionine are included in the positive list of Directive 2001/15/EC as acceptable sources for use in all foods for particular nutritional uses (FPNUs) (EC, 2001).

The US Food and Drug Administration (FDA) permits zinc DL-methionine to be added to foodstuffs as a food additive for human consumption [21CFR172.399] (FDA, 1981).

The SCF evaluated the general safety of using L-amino-acids in general and considered their use acceptable provided the addition to food does not give rise to a nutritional imbalance of the amino acids (SCF, 1990).

3. Biological and toxicological data

3.1. Bioavailability

3.1.1. Calcium L-methionate

As regards calcium L-methionate, the petitioner refers to a study by Heaney et al. (1990) on the fractional absorption of seven chemically defined calcium sources (i.e. calcium oxalate, calcium carbonate, calcium citrate, calcium bisglycinate, calcium citrate malate, tricalcium phosphate and hydroxyapatite) measured under standardized load conditions in a group of adult women (aged from 20 to 40 years). Solubility of the sources in water at neutral pH ranged from a low of 0.04 mM to a high of 1500 mM.

Data from this study also showed that the percentage absorption of calcium from the different sources varied between 44.0 ± 10.4 % (highest, Ca-bisglycinate) and 16.6 ± 9.0 % (lowest, hydroxyapatite) (Heaney et al., 1990).

Data from four food sources for calcium (spinach, bone meal/substance, milk and kale) are presented by the petitioner for comparison. Absorption of food calcium was not clearly related to the absorption of the dominant chemical form in the food concerned. These findings suggest that even under controlled, chemically defined conditions, solubility of a source has very little influence on its absorption and that absorption of calcium from food sources is determined mainly by other food components.

The petitioner further expects the metabolic fate and biological distribution of calcium L-methionate to be similar to that for other sources of calcium in the diet as the source is expected to dissociate before absorption.

3.1.2. Magnesium L-methionate

As regards magnesium L-methionate no specific data are provided by the petitioner. The petitioner only states that this source like some other magnesium salts of organic acids is...
Calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate added for nutritional purposes to food supplements

highly water soluble and readily absorbed in the intestine. According to the EVM (2003) the net absorption of magnesium from the diet is typically approximately 50%.

3.1.3. Zinc mono-L-methionine sulphate

One petitioner provides data on the bioavailability of zinc mono-L-methionine sulphate from human studies, animal studies and supplementation studies with livestock.

3.1.3.1. Human studies

The petitioner refers to a study by Rosado et al. (1993) on the bioavailability of zinc from zinc monomethionine sulphate compared with zinc sulphate and zinc polyascorbate. Nine (9) healthy adult volunteers received 25 mg of zinc in three different supplements, either alone in a water solution or added to a standard meal (SM). All subjects were also studied with water alone and SM alone, as controls. The SM contained plant foods that are habitually consumed in rural Mexico (i.e. corn ‘tortillas’, black beans, lettuce, tomato, orange, vegetable oil and corn beverage ‘atole’). When the supplements were given with water, the area under the curve (AUC) for the 4-h observation was: 262 ± 30 µg/dL for zinc methionine, 225 ± 9 µg/dL for zinc polyascorbate, 210 ± 33 µg/dL for zinc sulphate and 1 ± 6 µg/dL for water. Plasma zinc increased to a greater extent after zinc monomethionine sulphate than after zinc sulphate (p<0.05). Ingestion of the SM alone produced a significant reduction in plasma zinc compared to fasting levels (AUC = -50 ± 9 µg/dL).

Rosado et al. (1997) also carried out a double-blind, randomized community trial with 219 Mexican preschoolers (about 28 months of age, average body weight 11.1 kg) supplemented with a 20 mL solution containing either 20 mg zinc as zinc methionine, 20 mg iron as iron(II) sulphate, 20 mg zinc + 20 mg iron, or a placebo. After 12 months, plasma zinc increased significantly in the two zinc-treated groups: respectively 16.8 ± 0.8 µM zinc/L (p < 0.01) in the zinc group and 18.3 ± 0.7 µM zinc/L (p < 0.01) in the zinc + iron group compared to 14.4 ± 0.6 µM zinc/L in the placebo group). There was no effect of treatments in growth rate or body composition.

3.1.3.2. Animal studies

Beutler et al. (1998) studied the equivalent uptake of organic (zinc methionate sulphate and zinc propionate) and inorganic zinc (zinc chloride) by monkey kidney fibroblasts, human intestinal epithelial cells and perfused mouse intestine. The study showed equivalent uptakes of zinc from inorganic and organic compounds indicating that zinc from zinc methionate sulphate is bioavailable.

The petitioner also provided data of a number of supplementing studies with livestock investigating the bioavailability of zinc:

Studies in pigs

Wedekind et al. (1994) assessed the bioavailability of zinc from inorganic and organic zinc sources in weanling pigs. Zinc was shown to be bioavailable but its bioavailability was source
Calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate added for nutritional purposes to food supplements

dependent with the following ranking in bioavailability: zinc sulphate > zinc methionate > zinc oxide > zinc lysinate.

These findings were confirmed in a study by Schell and Kornegay (1996).

Rupic et al. (1997) studied the nutritional efficiency of dietary zinc from either zinc sulphate or zinc methionate in zinc-depleted pigs (depletion period: 30 days). From the study it was concluded that the bioavailability of zinc from zinc methionate was better than that from zinc sulphate, particularly in the period of rapid growth.

Studies with ruminants
The petitioner further provided data derived from bioavailability studies of zinc from zinc methionate and zinc oxide in lambs and cattle (Spears, 1989) and from zinc methionine, zinc sulphate and zinc oxide in cattle (Rojas et al., 1996). The studies show that also in ruminants zinc is bioavailable from these sources.

3.2. Toxicological data

3.2.1. Metabolism and kinetics
The absorption and metabolic fate of magnesium, calcium and zinc cations has been detailed previously by the SCF and the EFSA (SCF, 1990; 2001; 2003a; 2003b) and has recently been compiled and evaluated by EFSA (2006).

3.2.2. Other toxicological information
The Panel notes that the SCF (1990) considered the use of L-amino acids generally acceptable provided that their addition to food does not give rise to a nutritional imbalance of the amino acids.

3.2.2.1. Calcium L-methionate
No specific data on the toxicity, carcinogenicity, genotoxicity or reproductive and developmental toxicity of calcium L-methionate as a source of calcium have been provided. The petitioner only refers to data on the toxicity of calcium itself derived from a number of studies with humans and animals. In these studies the sources of calcium were calcium carbonate or calcium lactate.

The Panel notes that the toxicity of the cation calcium has already been evaluated by other bodies (SCF, 1990; SCF, 2003a; EVM, 2003) and refers to these evaluations throughout this opinion.

3.2.2.2. Magnesium L-methionate
No specific data on the toxicity, carcinogenicity, genotoxicity or reproductive and developmental toxicity of magnesium L-methionate as a source of magnesium have been
provided. The petitioner only refers to data on the toxicity of magnesium itself derived from a number of studies with humans and animals. In these studies the sources of magnesium were magnesium chloride and magnesium sulphate.

The Panel notes that the toxicity of the cation magnesium has already been evaluated by other bodies (SCF, 1990; SCF, 2003a; EVM, 2003b) and refers to these evaluations throughout this opinion.

### 3.2.2.3. Zinc mono-L-methionine sulphate

The petitioner makes reference to a number of studies evaluating various mechanisms of action of zinc methionine in rats, poultry, sheep and cattle (Flora et al., 1991; Gilani et al., 1991; Gilani et al., 1994; Hatfield et al., 1995; Kidd et al., 1994a; Kidd et al., 1994b; Kienholz et al., 1992; Moreng et al., 1992; Nocek et al., 2000; Nockels et al., 1993; Seyoum and Persaud, 1993). However, none of the studies were designed to investigate toxicity.

According to one petitioner there has been a single chronic toxicity study in rats looking at the effects of supplementation with zinc methionine, chromium polynicotinate, and grape seed extract on various metabolic parameters in the rat. One hundred and four hybrid (Brown Norway/Fischer 344) rats were dosed after a weaning and acclimatisation period of 5 weeks. Two groups were examined. Group 1 received a baseline diet and Group 2 received a baseline diet supplement with chromium polynicotinate (5 mg/kg), zinc monomethionine (18 mg/kg) and grape seed extracts. At the end of the study, blood chemistry was measured. Also in the study randomly selected rats were used from each group for evaluation of lipid peroxidation/free radical formation (hepatic TBARS formation) and L-NAME challenge (effects of nitric oxide synthase inhibition on systolic blood pressure). Systolic blood pressure (SBP) measurements were made twice a week.

Body weight gains were virtually the same in the two groups over the one-year dietary study period. The weights of hearts, kidneys and livers were not significantly different among groups. However the weight of the epididymal fat pad was statistically significantly less at 12 months in Group 2 in comparison to the control. Almost from the initiation of the dietary intervention, the SBP measurements of Group 2 were statistically significantly less compared to Group 1 (control). Hepatic TBARS formation, an estimate of lipid peroxidation was significantly lower after 1 year in Group 2 and HbA1C was also statistically significantly lower in Group 2 in comparison to the control. The authors concluded that no signs of toxicity were noted (Preuss et al., 2001).

The Panel notes however that the results summarised above are derived from a combination study and therefore no conclusion on the safety assessment for zinc-methionate alone can be drawn.

### 3.2.3. Non-clinical studies on zinc mono-L-methionine sulphate

The petitioner refers to a zinc and iron supplementation study carried out in young children in Mexico (Rosado et al., 1997) already referred to in section 3.1.3 of this opinion. Zinc methionine was selected as the best means of zinc supplementation based on the results of a previous study carried out by the same authors (Rosado et al, 1993).
As already described, in a double-blind, randomised community trial 219 Mexican preschoolers (age 18 to 36 months) were supplemented with either 20 mg zinc as zinc methionine, 20 mg iron as iron(II) sulphate, 20 mg Zinc + 20 mg iron, or a placebo. A solution containing sugar, citric acid, water and flavouring was used to prepare all the supplements. Children in each group received the supplements for 12 months (compliance was 97%). Data from 25 children were not included in the analyses as they dropped out of the study primarily because of a changing family situation. Height and other physical measurements were carried out at baseline and at 6 and 12 months. Similarly a clinical examination was conducted by a physician, at baseline and at 6 and 12 months. Morbidity was assessed twice weekly by questionnaire. A fasted blood sample was taken at baseline and at 6 and 12 months. Plasma zinc and plasma ferritin were measured by atomic absorption spectroscopy and radioimmunoassay respectively. There were no significant differences noted in growth and body composition data.

After 12 months, plasma zinc increased significantly in the two zinc-treated groups, and plasma ferritin was significantly higher in the two iron-treated groups (Table 4).

Table 4. Changes (mean ±SEM) in biochemical indicators between baseline and 12 months of supplementation.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Iron</th>
<th>Zinc</th>
<th>Zinc + Iron</th>
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</thead>
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<tr>
<td></td>
<td>0 months</td>
<td>12 months</td>
<td>0 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Hb (g/L)</td>
<td>108±14</td>
<td>118±8</td>
<td>108±13</td>
<td>118±9</td>
</tr>
<tr>
<td>Hb (g/L)</td>
<td></td>
<td>109±11</td>
<td>108±7</td>
<td>107±10</td>
</tr>
<tr>
<td>Ferritin (μg/L)</td>
<td>20.1±44.6</td>
<td>22.9±16.5</td>
<td>46.9±24.2*</td>
<td>18.9±15.8</td>
</tr>
<tr>
<td>Ferritin (μg/L)</td>
<td></td>
<td>19.7±13.5</td>
<td>14.7±15.6</td>
<td>14.7±15.6</td>
</tr>
<tr>
<td>Zinc (μmol/L)</td>
<td>14.2±0.7</td>
<td>14.4±0.6</td>
<td>15.2±0.6</td>
<td>15.2±0.7</td>
</tr>
<tr>
<td>Zinc (μmol/L)</td>
<td></td>
<td>13.2±0.6</td>
<td>16.8±0.8**</td>
<td>16.5±0.6</td>
</tr>
<tr>
<td></td>
<td>14.7±22.9**</td>
<td></td>
<td></td>
<td>18.3±0.7**</td>
</tr>
</tbody>
</table>

* P<0.05, ** P<0.01, ***P<0.001

Zinc and zinc+iron supplements reduced morbidity but had no effect on growth or body composition.

3.2.4. Toxicity of L-methionine

Garlick (2006) carried out a literature search to identify evidence relating to the possible toxicity of methionine in human subjects. According to this author, methionine, including the D and DL isomers, in amounts both below and above the requirement has been evaluated in nutritional and metabolic studies. The daily requirement for methionine was set at 10 mg/kg bw/day (FAO/WHO/UNO, 2002). No adverse effects in adults and children have been reported. Although methionine is known to aggravate psychopathological symptoms in schizophrenic patients, there is no evidence of similar effects in healthy subjects (Cohen et al., 1982).

The role of methionine as a precursor of homocysteine is the most notable cause for concern. A "loading dose" of 100 mg methionine/kg bw (6 g/day for a 60 kg person) given daily for 1
Calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate added for nutritional purposes to food supplements

week resulted in an acute increase in plasma homocysteine, an index of susceptibility to cardiovascular disease. Although this procedure resulted in vascular dysfunction, the effect was considered as an acute effect and unlikely to result in permanent damage (McAuley et al., 1999).

From the literature search by Garlick (2006), it also appears that methionine-loading tests have been performed on at least 6000 adults without any serious adverse effects being reported. However, Cottington et al. (2002) reported one case where a dose of 1 g/kg bw/day (60 g/day for a 60 kg person) was given mistakenly to a female adult, resulting in death.

Longer-term studies in adults have indicated no adverse consequences of moderate fluctuations in dietary methionine intake, but intakes higher than 5 times normal (normal intakes being estimated at approximately 2.5 g methionine/day) resulted in elevated homocysteine levels. These effects of methionine on homocysteine and vascular function are moderated by supplements of vitamins B₆, B₁₂, C, and folic acid (Brattström, 1996).

In infants, methionine intakes in the range of 125–507 mg/kg bw/day (equivalent to about 2 g/day to 8 g/day for 15 kg infant) resulted in impaired growth and extremely high plasma methionine levels, but no adverse long-term consequences were observed (Mudd, 2003).

4. Discussion

The Panel noted that for calcium L-methionate and magnesium L-methionate no specific data demonstrating the bioavailability of the cations calcium and magnesium from these sources have been provided. However, data from studies on the bioavailability of related sources of calcium and magnesium (i.e. salts of organic acids and amino acids) have shown the cations to be bioavailable. Calcium L-methionate and magnesium L-methionate are expected to dissociate before absorption and to be readily absorbed in the intestine. The bioavailability of zinc from zinc mono-L-methionine sulphate has been demonstrated based on studies in humans, animals and supplementation studies with livestock.

Methionine is found in different food sources at levels between 530 mg/kg (spinach) and 5470 mg/kg (soybeans).

In the case of calcium L-methionate, the highest reported calcium content in single nutrient supplements and the most common multiple nutrient supplements on the market is 1200 mg. If all the calcium in food supplements were to be provided by the addition of calcium L-methionate, this would lead to a potential dietary exposure of about 8935 mg methionine/day, corresponding to 149 mg methionine/kg bw/day for a 60 kg person. Based on this information the Panel considers an exposure to 149 mg methionine/kg bw/day from calcium L-methionate to be a conservative estimate.

In the case of magnesium L-methionate, if all the magnesium in food supplements were to be provided by the addition of magnesium sulphate at the Tolerable Upper Intake Level (UL) of 250 mg magnesium/day, the equivalent exposure to methionine would be 3069 mg/day, corresponding to 51 mg methionine/kg bw/day for a 60 kg person. Based on this upper limit for supplemental magnesium, the Panel considers an exposure to 51 mg methionine/kg bw/day from magnesium L-methionate as a conservative estimate.

In case of zinc mono-L-methionine sulphate, if all the zinc in food supplements were to be provided by the addition of zinc mono-L-methionine sulphate at the UL of 25 mg zinc per day, the potential exposure to methionine would be 57.2 mg methionine /day corresponding to
about 0.95 mg methionine/kg bw/day for a 60 kg person. Based on this UL for zinc, the Panel considers an exposure to 0.95 mg methionine/kg bw/day as a conservative estimate.

Under the same assumption as above the exposure to sulphate from the addition of zinc mono-L-methionine sulphate would be 73 mg sulphate/day, equivalent to 1.2 mg sulphate/kg bw/day for a 60 kg person. The Panel previously evaluated the safety of sulphate from calcium sulphate as the source and came to the conclusion that a daily intake of the sulphate ion up to a level of 6 g/day (100 mg sulphate/kg bw/day) does not raise a safety concern (EFSA, 2008). Based on this previous evaluation the Panel concludes that exposure to 1.2 mg sulphate/kg bw/day resulting from the proposed uses and use levels of zinc L-methionine sulphate as a source of zinc is of no safety concern.

The Panel notes that if in a multivitamin supplement all calcium, magnesium and zinc at the above listed levels were to be provided as methionate this would result in a methionine intake of (149 mg/kg bw/day + 51 mg/kg bw/day + 0.95 mg/kg bw/day for a 60 kg person) about 200 mg methionine/kg bw/ or 12 g/day for a 60 kg person.

A dose of methionine of 100 mg/kg bw (i.e. 6 g for a 60 kg person) resulted in an acute increase in plasma homocysteine. A dose of 1 g/kg bw (i.e. 60 g for a 60 kg person) given in error resulted in death while methionine intakes 5 times higher than normal (i.e. intakes approximately 12.5 g methionine/day; normal intakes being estimated at about 2.5 g methionine/day) resulted in elevated homocysteine levels. However, longer-term studies in adults indicated no adverse effects of moderate fluctuations in dietary methionine intake. In line with the SCF, 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 the use of methionine sources at these levels, together giving rise to a methionine intake of 12 g per day for a 60kg person, could be of safety concern.

The Panel notes that if all the calcium in food supplements were to be provided by the addition of calcium L-methionate at the UL of 1200 mg this would lead to a potential dietary exposure of about 9 g methionine/day for an adult. The Panel further notes that this would be an additional exposure above the normal intake of methionine via the diet (i.e. about 2.5 g/day) resulting in a total intake of about 11.5 g methionine/day. The Panel has no data demonstrating that such a level of intake would be safe.

The Panel also notes that if all the magnesium in food supplements were to be provided by the addition of magnesium L-methionate at the UL of 250 mg magnesium/day this would lead to a potential exposure of about 3 g methionine/day resulting in a total methionine intake (supplemental + dietary) of about 5.5 g/day. Based on the same considerations as above the Panel has no data to prove that this would be a safe level of intake.

The Panel notes that in the case of zinc mono-L-methionine sulphate if all the zinc in food supplements were to be provided by the addition of zinc mono-L-methionine sulphate at the UL of 25 mg zinc per day the potential exposure to methionine would be 57.2 mg methionine /day. The Panel considers this level of methionine intake to be of no safety concern.

Although the safety of zinc itself, in terms of amounts that may be consumed, is outside of its remit, the Panel wants to indicate that, at the 97.5th percentile the dietary zinc intake from total food only is already close to the UL as established by the SCF. The addition of the intake of zinc from food supplements and/or fortified food to the normal zinc intake could lead to an exceeding of the UL especially for consumers at high percentiles.
CONCLUSIONS

The present opinion deals only with the safety of calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate as sources for respectively calcium, magnesium and zinc added for nutritional purposes to food supplements. The safety evaluation of calcium, magnesium and zinc are outside the remit of this Panel.

The Panel concludes that the bioavailability of calcium, magnesium and zinc from calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate is expected to be similar to that of other comparable sources of these nutrients.

In the absence of data that demonstrate the safety of the potential total exposure to about 11.5 g methionine/day resulting from intakes of both calcium L-methionate supplements and from the diet and to a potential total exposure of about 5.5 g methionine/day from both magnesium L-methionate supplements and from the diet, the Panel concludes that the use of calcium methionate and magnesium methionate as sources for calcium and magnesium at the proposed use levels could be of safety concern.

The Panel further concludes that in case of zinc mono-L-methionine sulphate, the potential exposure to methionine and sulphate is negligible compared to the normal dietary intake of these compounds, and that the use of zinc mono-L-methionine sulphate at the proposed level of use as a source of zinc is not of safety concern.
Calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate added for nutritional purposes to food supplements

**DOCUMENTATION PROVIDED TO EFSA**


**REFERENCES**


EFSA, 2006. Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to Calcium, Magnesium and Zinc Malate added for nutritional purposes to food supplements as sources for Calcium, Magnesium and Zinc and to Calcium Malate added for nutritional purposes to foods for particular nutritional uses and foods intended for the general population as source for Calcium. The EFSA Journal (2006) 391 a,b,c,d, 1-6.


Flora SJS, Kumar D, Gupta SD, 1991. Interaction of zinc, methionine or their combination with lead at gastrointestinal or post-absorptive levels in rats. Pharmacology and Toxicology 68 (1), p3-7.


Calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate added for nutritional purposes to food supplements


Calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate added for nutritional purposes to food supplements


**GLOSSARY / ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AI</td>
<td>Adequate Intakes</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under Curve</td>
</tr>
<tr>
<td>bw</td>
<td>body weight</td>
</tr>
<tr>
<td>CAS No</td>
<td>Chemical Abstracts Service Registry Number</td>
</tr>
<tr>
<td>EC</td>
<td>European Commission</td>
</tr>
<tr>
<td>ESADDI</td>
<td>Estimated Safe and Adequate Daily Dietary Intakes</td>
</tr>
<tr>
<td>EVM</td>
<td>UK Expert Group on Vitamins and Minerals</td>
</tr>
<tr>
<td>FAO</td>
<td>Food and Agricultural Organisation</td>
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<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
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<tr>
<td>FPNU</td>
<td>Foods for Particular Nutritional Uses</td>
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<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
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<tr>
<td>ICP</td>
<td>Inductively Coupled Plasma</td>
</tr>
<tr>
<td>IOM</td>
<td>Institute of Medicine</td>
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<tr>
<td>IR</td>
<td>Infrared</td>
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<tr>
<td>L-NAME</td>
<td>N-Nitro-L-Arginine Methyl Ester</td>
</tr>
<tr>
<td>NHANES</td>
<td>US National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>PRI</td>
<td>Population Reference Intake</td>
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<tr>
<td>RDI</td>
<td>Recommended Daily Intake</td>
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<tr>
<td>RNI</td>
<td>Reference Nutrient Intake</td>
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<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
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<tr>
<td>SCF</td>
<td>Scientific Committee for Food</td>
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<tr>
<td>SEM</td>
<td>Standard Error of the Mean</td>
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<td>SM</td>
<td>Standard Meal</td>
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<tr>
<td>TBARS</td>
<td>Thiobarbituric Acid Reactive Substances</td>
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<tr>
<td>UL</td>
<td>Tolerable Upper Intake Level</td>
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<td>UNO</td>
<td>United Nations Organisation</td>
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