Opinion on certain bisglycinates as sources of copper, zinc, calcium, magnesium and glycinate nicotinate as source of chromium in foods intended for the general population (including food supplements) and foods for particular nutritional uses

Scientific Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food


Adopted on 22 May 2008

PANEL MEMBERS

SUMMARY
Following a request from the European Commission, the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) was asked to deliver a scientific opinion on the use of copper bisglycinate chelate and chromium glycinate nicotinate as sources for respectively copper and chromium added for nutritional purposes to food supplements, and of calcium bisglycinate chelate and magnesium bisglycinate chelate as sources for respectively calcium and magnesium added for nutritional purposes to foods for particular nutritional uses and food supplements, and of zinc bisglycinate chelate when used as a source for zinc in foods intended for the general population (including food supplements) and foods for particular nutritional uses.

The mineral amino acid chelates considered in this application are intended for use as a direct replacement for the permitted respective mineral forms of copper and chromium for nutritional purposes in food supplements according Council Directive 2002/46/EC, for calcium and magnesium for nutritional purposes in food supplements and the categories of PARNUTS other than for baby foods and infant formula according to Council Directive 89/398/EEC, and for zinc in foods intended for the general population (including food supplements) and foods for particular nutritional uses.

1 For citation purposes: Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission on certain bisglycinates and glycinate nicotinate as sources for copper, zinc, calcium, magnesium and chromium. The EFSA Journal (2008) 718, 1-266.

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The present opinion deals only with the safety of bisglycinate chelates of copper, zinc, calcium, magnesium, and of glycinate nicotinate as sources of the nutrient cations of respectively copper, zinc, calcium, magnesium and chromium and with the bioavailability of the nutrient cations from these sources. The safety of the nutrient cations themselves (copper, chromium, zinc, calcium and magnesium), in terms of amounts that may be consumed, is outside the remit of this Panel.

The bisglycinates considered in this opinion consist of a bivalent metal ion, namely Cu$^{+2}$, Zn$^{+2}$, Ca$^{+2}$, and Mg$^{+2}$, linked to two molecules of glycine. The metal is bound to the carboxyl group and to the α-amino group of glycine with coordinate covalent bonds to form two heterocyclic rings. This 1:2 metal to ligand ratio restricts reaction with dietary inhibitors of the metal absorption and does not participate in oxidation reactions.

Chromium(III) glycinate nicotinate chelate is also considered in this opinion.

No specific use levels for the mineral bisglycimates under consideration in this opinion have been given. However, it is assumed that under the intended conditions of use, the daily intake would not exceed those levels anticipated through existing supplementation of the listed minerals and would be similar to other forms of copper, zinc, calcium, magnesium and chromium that are already approved for use in foods in the EU.

Regarding the bioavailability of the different cations from their sources, data are provided showing that the minerals are bioavailable after oral administration.

No genetic toxicity studies have been conducted on the compounds; however the Panel has no concern on the genotoxicity aspects of glycine or nicotinic acid.

Due to the similarity in chemical structure between the metal glycines considered in the present application and ferrous bisglycinate it is anticipated that the glycine part of these glycines will exhibit similar toxicological characteristics as their ferrous bisglycinate counterpart, the safety of which was already evaluated and accepted by the AFC Panel in 2006. The Panel agrees that the subchronic studies on ferrous bisglycinate can be used to assess the subchronic toxicity of the glycines. From the studies a NOAEL of 500 mg/kg body weight/day for ferrous bisglycinate in rats (the highest dose tested) was derived, corresponding to approximately 400 mg glycinate/kg body weight/day.

Specific chronic toxicity or carcinogenicity studies are not available.

Specific reproductive toxicity and developmental toxicity studies on the bisglycinates are also not available. However, in longer-term feeding studies with livestock (female pigs) receiving dietary supplementation with mineral glycines throughout a period covering multiple litters, no adverse effects on reproduction or on the resulting offspring were observed.

The Panel noted that these longer-term feeding studies are of limited value for the assessment of either chronic toxicity or carcinogenicity of the chelates, due to the relatively short duration of the studies relative to the life span of the pig and the small numbers of animals used in the studies.

A conservative estimate of the dietary exposure was made based on a hypothetical intake from all sources (PARNUTS, food supplements and foods intended for the general population) at the tolerable upper intake level for copper (5 mg/day), zinc (25 mg/day), calcium (2500 mg/day) and magnesium (250 mg/day). The equivalent exposure to glycine would be around 12 mg glycine/day for copper bisglycinate, 57 mg glycine/day for zinc bisglycinate, 9239 mg glycine/day for calcium bisglycinate and 1523 mg glycine/day for magnesium bisglycinate. The Panel noted that this estimated exposure is lower than the NOAEL of 400 mg glycinate/kg bw/day, the highest dose tested.
In addition the normal (mean) intake of glycine in proteins from both food of animal origin, and vegetable origin was calculated to be about 26 mg/kg bw/day for adults (>15 years) and to about 43 mg/kg bw/day for children (<15 years).

Glycine (synthetic or natural) is already permitted in the EU for use in foods under Directive 2001/15/EC on substances that may be added for specific nutritional purposes in foods for particular nutritional uses (PARNUTS). Glycine and its salts (E640) have an ADI not specified and are permitted as food additives in the EU under Directive 95/2/EC on food additives other than colours and sweeteners.

The Panel concludes that the use of copper bisglycinate chelate as a source for copper added for nutritional purposes to food supplements, and of calcium bisglycinate chelate and magnesium bisglycinate chelate as sources for respectively calcium and magnesium added for nutritional purposes to foods for particular nutritional uses and food supplements, and of zinc bisglycinate chelate when used as a source for zinc in foods intended for the general population (including food supplements) and foods for particular nutritional uses, is not of safety concern.

As regards chromium glycinate nicotinate complex, due to lack of information on the specific identity of its components, the Panel is unable to reach a conclusion on the safety of this source and on the bioavailability of chromium from this source.

Keywords:

Copper bisglycinate chelate, CAS N° 13479-54-4; Zinc bisglycinate chelate, CAS N° 14281-83-5; Zinc Glycinate, CAS N° 14281-83-5; Calcium bisglycinate chelate; CAS N° 56960-17-9; Magnesium bisglycinate chelate, CAS N° 14738-68-7; Chromium glycinate nicotinate hydrochloride.
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Opinion on certain bisglycinates as sources of copper, zinc, calcium, magnesium and bisglycinate nicotinate as source of chromium
Opinion on certain bisglycinates as sources of copper, zinc, calcium, magnesium and bisglycinate nicotinate as source of chromium

BACKGROUND AS PROVIDED BY THE EUROPEAN 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 certain amino acid chelates as sources of certain minerals in foods for particular nutritional uses and in foods for the general population (including food supplements).

The relevant European legislative measures identified by the petitioner are:

- Commission Directive 2001/15/EC on substances that may be added for specific nutritional purposes in foods for particular nutritional uses\(^2\).
- Regulation EC 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods\(^4\).

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN 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 scientific opinions, based on its consideration of the safety and bioavailability of:

- copper bisglycinate and chromium glycinate nicotinate hydrochloride when added to food supplements,
- calcium bisglycinate and magnesium bisglycinate when added for nutritional purposes in foods for particular nutritional uses and food supplements,
- zinc bisglycinate when used as a source for zinc in foods intended for the general population (including food supplements) and foods for particular nutritional uses.

ACKNOWLEDGEMENTS

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


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\(^2\) OJ No L 52, 22.2.2001, p.19.
\(^3\) OJ No L 183, 12.7.2002, p. 51.
ASSESSMENT

1. Introduction
The present opinion deals only with the safety of bisglycinate chelates of copper, zinc, calcium, magnesium, and of glycinate nicotinate as sources of the nutrient cations of respectively copper, zinc, calcium, magnesium and chromium and with the bioavailability of the nutrient cations from these sources. The safety of the nutrient cations themselves (copper, chromium, zinc, calcium and magnesium), in terms of amounts that may be consumed, is outside the remit of this Panel.

2. Chemistry
Metal bisglycinates consist of a bivalent metal ion (M^{2+}) linked to two molecules of glycine. The metal is bound to the carboxyl group and to the α-amino group of glycine with coordinate covalent bonds as described by McMurray and Fay (1995), to form two heterocyclic rings (Atkins and Beran, 1992; Ashmead, 2001). According to Jeppsen (2001) and to Allen (2002), this 1:2 metal to ligand ratio restricts reaction with dietary inhibitors of the metal absorption and prevents the metal from participating in oxidation reactions.

*General molecular Formula:* M(COOCH₂NH₂)₂

In the structural formula, ‘M’, represents the ions Copper(II), Zinc(II), Calcium(II) or Magnesium(II).

Unlike the bisglycinates with bivalent cations, in chromium glycinate nicotinate chelate two molecules of chromium(III) are linked to three molecules of glycine and three molecules of nicotinic acid, chromium being a trivalent cation Cr(III). The structural formula as proposed by the petitioner is as follows:
In this formula ‘b’ represents 1-3 moles of niacin and ‘a’ represents 1-3 moles of glycine.

2.1 Identity of the substances

2.1.1. Copper bis(glycinate-N,O), CAS Number 13479-54-4

*Molecular Formula:* \( \text{Cu(COOCH}_2\text{NH}_2)_2 \); molecular weight (Mw): 211.68 Dalton

Two commercial food-grade products of copper bisglycinate were considered by the Panel. Product 1 is a formulation of copper bisglycinate with approved food additives. The exact composition of the formulation is known to the Panel. The copper content in this product is not less than 10%.

Product 2 is at least 98% pure copper bisglycinate on a dry weight basis.

Copper bisglycinate and the commercially available products are hygroscopic blue powders, freely soluble in water and practically insoluble in ethanol and acetone.

Proposed Chemical Specifications

The limits for heavy metals for the products as proposed by the petitioners are given in Table 2.1.1

<table>
<thead>
<tr>
<th>Test</th>
<th>Product 1</th>
<th>Product 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>Less than 1.5 mg/kg</td>
<td>Less than 5 mg/kg</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Less than 0.5 mg/kg</td>
<td>Not given</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Not given</td>
<td>Less than 3 mg/kg</td>
</tr>
<tr>
<td>Mercury</td>
<td>Not given</td>
<td>Less than 1 mg/kg</td>
</tr>
</tbody>
</table>

For Product 1 analysis data of 7 non-consecutive batches of the commercial formulation of copper bisglycinate shows that the copper content varies between 10.7 and 11.5 %, lead between < 0.1 and 0.26 mg/kg and that the cadmium content is always < 0.1 mg/kg.

For Product 2 no analysis data of batches have been provided by the petitioner.
2.1.2. Zinc bisglycinate, CAS number, 14281-83-5,

*Molecular Formula:* Zn(COOCH₂NH₂)₂; molecular weight (Mw): 213.53 Dalton

Three commercial food-grade products of zinc bisglycinate were considered by the Panel. Product 1 and Product 2 are a formulation of zinc bisglycinate with approved food additives. The exact composition of the formulations is known to the Panel. The zinc content in Product 1 is not less than 20% and not less than 10% in Product 2.

Product 3 is at least 98% pure zinc bisglycinate on a dry weight basis.

Zinc bisglycinate is freely soluble in water and practically insoluble in ethanol and acetone.

*Proposed Chemical Specifications*

The limits for heavy metals for the products as proposed by the petitioners are given in Table 2.1.2

<table>
<thead>
<tr>
<th>Test</th>
<th>Product 1</th>
<th>Product 2</th>
<th>Product 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead (mg/kg)</td>
<td>Less than 5 mg/kg</td>
<td>Less than 2 mg/kg</td>
<td>Less than 5 mg/kg</td>
</tr>
<tr>
<td>Cadmium (mg/kg)</td>
<td>Less than 5 mg/kg</td>
<td>Less than 1 mg/kg</td>
<td>Not given</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Not given</td>
<td>Not given</td>
<td>Less than 5 mg/kg</td>
</tr>
<tr>
<td>Mercury</td>
<td>Not given</td>
<td>Not given</td>
<td>Less than 1 mg/kg</td>
</tr>
</tbody>
</table>

Analysis data of 7 non-consecutive batches of the commercial products show that, for Product 1, the zinc content varies between 20.3 and 22.6 %, lead, between 0.64 and 1.37 mg/kg and that the cadmium content is always < 0.1 mg/kg.

For Product 2 the zinc content varies between 10.9 and 11.1 %, lead between 0.64 and 1.63 mg/kg and that the cadmium content is also always < 0.1 mg/kg. All 7 batches analysed also pass for the test on colour, texture and scent.

For Product 3 no analysis data of batches have been provided by the petitioner.

2.1.3. Calcium bis(glycinate-N,O), CAS Number 56960-17-9

*Molecular Formula:* Ca(COOCH₂NH₂)₂; Molecular weight (Mw): 188.11 Dalton

Four commercial food-grade products of calcium bisglycinate were considered by the Panel. Products 1, 2 and 3 are formulations of calcium bisglycinate with approved food additives. The exact composition of the formulations is known to the Panel. The calcium content in these products is respectively not less than 18%, not less than 13% and not less than 13%.

Product 4 is at least 98% of calcium bisglycinate on a dry weight basis.

Calcium bisglycinate is soluble in water, and practically insoluble in ethanol and acetone.
**Proposed Chemical Specifications**

The limits for heavy metals for the products as proposed by the petitioners are given in Table 2.1.3

### Table 2.1.3 Proposed limits for heavy metals for Calcium bisglycinates

<table>
<thead>
<tr>
<th>Test</th>
<th>Product 1</th>
<th>Product 2</th>
<th>Product 3</th>
<th>Product 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>Less than 0.5 mg/kg</td>
<td>Less than 0.5 mg/kg</td>
<td>Less than 0.5 mg/kg</td>
<td>Less than 5 mg/kg</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Less than 0.5 mg/kg</td>
<td>Less than 0.5 mg/kg</td>
<td>Less than 0.5 mg/kg</td>
<td>Not given</td>
</tr>
<tr>
<td>Mercury</td>
<td>Not given</td>
<td>Not given</td>
<td>Not given</td>
<td>Less than 1 mg/kg</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Not given</td>
<td>Not given</td>
<td>Not given</td>
<td>Less than 3 mg/kg</td>
</tr>
</tbody>
</table>

Analyses data of 7 non-consecutive batches of the commercial products show that, for Product 1 the calcium content varies between 19.0 and 21.1 %, and the content of lead and cadmium always <0.1 mg/kg.

For Product 2 the calcium content varies between 13.9 and 16 %; for lead and cadmium the content is always <0.1 mg/kg.

For Product 3 the calcium content varies between 26.8 and 30.0%, lead between 0.16 and 0.2 mg/kg and for cadmium between < 0.1 and 0.27 mg/kg.

For Product 4 no analysis data of batches have been provided by the petitioner.

### 2.1.4. Magnesium bis(glycinate-N,O), CAS Number 14783-68-7

**Molecular Formula:** \( \text{Mg} \left( \text{COOCH}_2\text{NH}_2 \right)_2 \); molecular weight (Mw) : 172.44 Dalton.

Four commercial food-grade products of magnesium bisglycinate were considered by the Panel. Products 1, 2 and 3 are formulations of magnesium bisglycinate with approved food additives. The exact composition of the formulations is known to the Panel. The magnesium content in these products is respectively not less than 10%, not less than 8% and not less than 18%.

Product 4 is at least 98% of magnesium bisglycinate on a dry weight basis.

Magnesium bisglycinate is freely soluble in water and practically insoluble in ethanol and acetone.

**Proposed Chemical Specifications**

The limits for heavy metals for the products as proposed by the petitioners are given in Table 2.1.4

### Table 2.1.4 Proposed limits for heavy metals for Magnesium bisglycinates

<table>
<thead>
<tr>
<th>Test</th>
<th>Product 1</th>
<th>Product 2</th>
<th>Product 3</th>
<th>Product 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>Less than 0.3 mg/kg</td>
<td>Less than 1.5 mg/kg</td>
<td>Less than 1.5 mg/kg</td>
<td>Less than 5 mg/kg</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Less than 0.5 mg/kg</td>
<td>Less than 0.5 mg/kg</td>
<td>Less than 0.5 mg/kg</td>
<td>Not given</td>
</tr>
</tbody>
</table>
Analysis data of 7 non-consecutive batches of the commercial products show that, for Product 1, the magnesium content varies between 10.9 and 11.9 %, for lead between < 0.1 and 0.14 mg/kg and for cadmium between <0.1 and 0.15 mg/kg.

For Product 2 the magnesium content varies between 8.28 and 8.93%, lead between <0.1 and 0.15 mg/kg and for cadmium always <0.1 mg/kg.

For Product 3 the magnesium content varies between 18.3 and 19.5%, for lead between < 0.1 and 0.12 mg/kg and for cadmium between < 0.1 and 0.19 mg/kg.

For Product 4 no analysis data of batches have been provided by the petitioner.

### 2.1.5. Chromium glycinate nicotinate chelate hydrochloride, CAS Number: None established

*Molecular Formula:* \( \text{Cr}_2(\text{COOCH}_2\text{NH}_2)_3(\text{C}_6\text{H}_5\text{NO}_2)_3 \) \( 6\text{HCl}, \text{Mw} 914.3 \text{ Dalton} \). The molecular weight of the active ingredient [i.e. \( \text{Cr}_2(\text{COOCH}_2\text{NH}_2)_3(\text{C}_6\text{H}_5\text{NO}_2)_3 \)] is 659.52 Dalton.

One commercial food-grade product was considered by the Panel. The product is a formulation of chromium glycinate nicotinate chelate hydrochloride with approved food additives. The composition of the formulation is known to the Panel, but the exact identity of the active ingredient is not known. The chromium content in this product is not less than 2.5%.

The commercially available chromium glycinate nicotinate chelate is a hygroscopic powder, soluble in water and practically insoluble in ethanol and acetone.

*Proposed Chemical Specifications*

The limits for heavy metals for the products as proposed by the petitioners are given in Table 2.1.5

<table>
<thead>
<tr>
<th>Test</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead (mg/kg)</td>
<td>Less than 1.5 mg/kg</td>
</tr>
<tr>
<td>Cadmium (mg/kg)</td>
<td>Less than 0.5 mg/kg</td>
</tr>
</tbody>
</table>

Analysis data of 7 non-consecutive batches of the commercial product shows that the chromium content varies between 2.66 and 2.99 % and lead and cadmium are always < 0.1 mg/kg.
2.2 Manufacturing processes

2.2.1. Introduction
The petitioners indicate that glycine and nicotinic acid used to chelate the different metal ions meets USP grade specifications and is equivalent to food-grade material. Glycine (synthetic or natural) is permitted in the EU for use in foods under Directive 2001/15/EC (EC, 2001) on substances that may be added for specific nutritional purposes in foods for particular nutritional uses (PARNUTS) (EC, 2001) for the foods for special medical purposes. Glycine and its salts (E640) are also permitted as food additives in the EU under Directive 95/2/EC on food additives other than colours and sweeteners (EC, 1995). The glycine used in the production of the bisglycinates conforms to the EU specification as declared within Commission Directive 2000/63/EC (EC, 2000) amending Directive 96/77/EC laying down specific purity criteria of food additives other than colours and sweeteners (EC, 1996, 2000). Other processing chemicals (pH adjustment, flow agents, etc.) meet specifications appropriate for food-use. All other ingredients used in the formulation of the commercial products, meet specifications appropriate for food-use.

2.2.2. Methods of Manufacturing
The details of the manufacturing processes for the commercial formulation of the chelates are given by the petitioners in the application dossiers. This is considered by the Panel to be sufficient.

2.3 Methods of analysis
The respective chelates are first digested under strong acidic conditions at temperatures between 95 and 130°C. The sample digest is then assayed for the different metals content using a calibrated and validated Inductively Coupled Plasma/Atomic Emission Spectrometry (ICP/AES). The methods are described in detail by the petitioner in the application dossier. Glycine can be identified as indicated in EU Commission Directive 2000/63/EC (EC, 2000).

2.4 Reaction and fate in foods
The petitioners provided only information related to the stability of the sources in food supplements. As regards copper bisglycinate, in a 17-month assay, there was no interaction reported between the contents of a capsule, which contained 0.45 to 0.55 mg copper as copper bisglycinate and other metal amino acid chelates of zinc, and iron at levels of 1.37 to 1.67, 0.86 to 1.05, and 1.8 to 2.2 mg, respectively, and 36 to 44 µg of chromium (as chromium glycinate nicotinate chelate).

Similarly, in a 17-month assay, there was no interaction reported between the contents of a capsule, which included 1.37 to 1.67 mg zinc as zinc bisglycinate and other metal amino acid chelates of copper, and iron (supplied as ferrous bisglycinate) at levels respectively of 0.45 to 0.55, 0.86 to 1.05, and 1.8 to 2.2 mg and of 36 to 44 µg of chromium as chelate product.

In both stability studies also a multivitamin preparation (Vitamins A, C, D and E, as well as the Vitamin B series) was included. The stability of the chelated products was demonstrated by a lack of interaction between the metal amino acid chelates and any of the components of the capsules, including the vitamins, which were reported to retain levels within the specifications of the USP for the duration of the study period (Ashmead and Ashmead, 1995).
Opinion on certain bisglycinates as sources of copper, zinc, calcium, magnesium and bisglycinate nicotinate as source of chromium

There are no specific data on stability in foods. However, based on the results of the stability studies of the sources in food supplements, interaction of the sources with food components is not to be expected.

3. Case of Need and Proposed Uses

According to the petitioner the forms or sources of minerals have a bearing on their relative bioavailability and toxicology/safety. A study by Hillman (1996) indicates that e.g., mineral oxides are less soluble than other sources of minerals and resist further digestion. They are usually less bioavailable than the more soluble/ionisable inorganic salts. Organic forms of minerals are often more bioavailable than inorganic salts.

The naturally occurring amino acids are ligands that confer both increased bioavailability and complete utilisability once within the body. Such chelates provide advantages over other synthetic ligands, such as EDTA, where it has been observed that the ligated material occurs intact in human urine or alternatively ligated to essential elements in the body, which can lead to the unnecessary removal of these essential compounds (Pineda et al., 1994).

Amino acid chelates are better absorbed than many other mineral sources (Heaney et al., 1990; Pineda et al., 1994; Bovell-Benjamin et al., 2000).

The mineral bisglycinates considered in this application are intended for use as a direct replacement for the permitted respective mineral forms of copper and chromium for nutritional purposes in food supplements according to Council Directive 178/2002, calcium and magnesium for nutritional purposes in food supplements and the categories of PARNUTS other than for baby foods and infant formula according to Council Directive 89/398/EEC and for zinc for nutritional purposes in foods for the general population (including food supplements) and PARNUTS.

According to the petitioners the amino acid chelates are used by food supplement manufacturers as an ingredient in tablets, caplets, capsules, chewable tablets, effervescent powders and liquids that are food supplements. The method of incorporation is determined by the individual manufacturers as appropriate for the particular type of finished products.

4. Exposure

No specific use levels for the amino acid chelates under consideration in this opinion have been given. Tolerable Upper Intake Levels have been established in adults for four of the minerals considered: 5 mg/day for copper (SCF, 2003a), 25 mg/day for zinc (SCF, 2003c), 2500 mg/day for calcium (SCF, 2003b), 250 mg/day for magnesium was established for readily dissociable magnesium salts (SCF, 2001). No Tolerable Upper Intake Level was established for chromium(III) but the SCF (SCF, 2003e) noted that no adverse effects were associated with supplementary intake of chromium up to 1 mg/day.

Anticipated levels of exposure to glycine were calculated based on these Tolerable Upper Intake Levels for copper, zinc, calcium and magnesium by considering that they would entirely be ingested in the bisglycinate form: 11.7 mg glycine/day for copper bisglycinate, 56.6 mg glycine/day for zinc bisglycinate, 9239 mg glycine/day for calcium bisglycinate and 1523 mg glycine/day for magnesium bisglycinate. An intake of 1 mg/day of chromium in the form of chromium glycinate nicotinate would give rise to an intake of about 3.3 mg nicotinic acid/day and to 2.2 mg glycine/day.

The intake of glycine from proteins in meat and seeds (soya, flax, canola) was also considered. Average percentages of glycine in proteins of 1% for meat and 6% for seeds are reported (Chung et al., 2005; Toldra et al., 1995). Based on these data and on French consumption data
(INCA survey, 2000) the average intake of glycine was calculated for both food of animal (pork and pork-based-products, chicken, fish, beef, poultry and game) and vegetal origin (soya shoots, soya desserts, tofu, soya drinks, soya sauce, canola oil). The Panel estimated a mean intake of 26.2 mg/kg bw/day for adults (≥ 15 years) with a 97.5th percentile of 54.7 mg/kg bw/day and a mean intake of 43.1 mg/kg bw/day for children (3 to 14 years) with a 97.5th percentile of 101.4 mg/kg bw/day was obtained.

5. Information on Existing Authorisations and Evaluations

According to the petitioners the amino acid chelates of copper, zinc, calcium, magnesium and chromium (III) are currently utilised for dietary supplements and/or food fortification in North America (United States, Canada); Latin America (Argentina, Brazil, Guatemala); Europe (Austria, Belgium, Czech Republic, Denmark, Finland, France, Portugal, Spain, Sweden, Germany, United Kingdom); and Asia (Taiwan, Thailand); as well as Australia, Pakistan and South Africa.

The substances are freely sold in the United States under the 1994 Dietary Supplement Health and Education Act (DSHEA) due to their long history of safe use.

Ferrous bisglycinate, meeting certain specifications, was evaluated by the EFSA (EFSA, 2006) as a source of iron in foods intended for the general population, food supplements, and foods for particular nutritional uses including foods intended for infants and young children, and it was concluded that these uses do not present a safety concern.

Glycine (synthetic or natural) is already permitted in the EU for use in foods under Directive 2001/15/EC on substances that may be added for specific nutritional purposes in foods for particular nutritional uses (PARNUTS). Glycine and its salts (E640) are also permitted as food additives in the EU under Directive 95/2/EC on food additives other than colours and sweeteners.

6. Biological and toxicological data

6.1 Biological data

One of the petitioners indicates that the metal amino acid chelates used in the studies described below contain, in part, amino acids derived from hydrolysed vegetable protein (soya). The petitioner also indicates that the manufacturing formulae for some of these products may also contain commercially available glycine. Where glycine is added by formulation for part of the chelating ligands, an increased potential to create metal bisglycinate chelates is achieved.

6.1.1 Bioavailability of the mineral-bisglycinates following oral consumption

A study by Kirchhoff (1983) showed that the absorption of minerals presented as chelates is more effective than minerals that are present in the cationic state. This seems to be due to the fact that cationic minerals must be chelated by proteins in the cell wall prior to absorption, thus slowing down the process. No additional chelation of the amino acid chelates is required at the brush border of the cell membrane thus making the membrane transport more rapid.

6.1.1.1 Copper bisglycinate

In in vitro studies in rat jejunal slices on the absorption of copper contained in inorganic compounds was compared with chelates from hydrolysed protein sources.
The rats were previously maintained on a commercial diet adequately fortified with copper to ensure no forced tissue uptake of minerals. The slices were incubated with solutions of inorganic copper sources or copper amino acid chelate, utilising ligands derived from plant (soy) and casein proteins. The chelated copper and the inorganic salts contained an equivalent mineral concentration.

The results showed that the uptake of copper from the amino acid chelate (from plant origin) was 35 mg copper/kg as compared to the uptake of 8 mg copper/kg from copper sulphate, 11 mg copper/kg from copper oxide, 12 mg copper/kg from copper carbonate. Control values (trace values) were well below the values obtained for tissue samples incubated with the respective chelated or inorganic mineral solutions (Ashmead et al., 1985).

A study in humans (23 patients: 6 males, 17 females) was conducted on the effect of copper amino acid chelate supplementation on superoxide dismutase (SOD) in rheumatoid arthritis patients. The participants ranged in age from 35 to 53 years and were suffering from rheumatoid arthritis. Forty-eight healthy age-matched individuals were also selected to serve as a control group. Blood samples were taken to determine baseline mineral levels. Participants were then given 2 mg of copper amino acid chelate per day for 4 weeks. After the treatment an analysis of Cu-Zn SOD activity was carried out in the blood.

The results showed that the copper amino acid chelate supplementation increased erythrocyte Cu-Zn SOD activity in 18 of 23 rheumatoid arthritis patients. The average increase was 21%, showing that the copper chelate was absorbed and was effective in increasing erythrocyte Cu-Zn SOD activity in the majority of rheumatoid arthritis patients (DiSilvestro et al., 1992).

6.1.1.2. Zinc bisglycinate

In an in vitro study analogous with the one described above for copper, rat jejunal slices obtained from Sprague-Dawley rats were incubated for equal times with solutions of inorganic zinc sources or with zinc amino acid chelate utilising ligands derived from plant (soy) protein. The chelated zinc and the inorganic zinc salts contained an equivalent mineral concentration. After incubation, washing and drying, the tissue samples were analysed for metal content and were compared to untreated intestinal segment controls.

The results showed that the intestinal uptake of zinc was considerably greater for the zinc amino acid chelate solution (i.e. 191 mg Zn/kg) compared to the uptake from zinc sulphate (84 mg Zn/kg), zinc oxide (66 mg Zn/kg) or zinc carbonate (87 mg Zn/kg). Control values (14 mg Zn/kg) were well below the values obtained for tissue samples incubated with the respective chelated or inorganic mineral solutions (Ashmead et al., 1985).

Several studies in animals regarding the uptake of zinc from zinc amino acid chelate have been conducted.

In an in vivo study with Albino rats the extent of absorption of zinc from radiolabelled zinc ($^{65}$Zn) amino acid chelate was compared to its uptake from zinc chloride. In the study the rats received the same amount of radioactive zinc, either as zinc chloride or as $^{65}$Zn chelate, by gavage. After dosing, the rats were placed in metabolic cages on a normal diet (commercial rat chow) and observed for one week during which time the faeces were collected. The rats were then sacrificed and total radioactivity present in the faeces of each rat was measured.

The results showed that during the 7-day period more than 50% of the $^{65}$ZnCl$_2$ was excreted in the faeces. In comparison, only 12% of the radiolabelled $^{65}$Zn amino acid chelate was excreted during the same time period. The results indicate that the zinc amino acid chelate was retained within the animal significantly better than the $^{65}$ZnCl$_2$ group (Ashmead et al., 1975).
Another *in vivo* study was carried out to compare the rate of absorption and length of time for incorporation of $^{65}$Zn amino acid chelate versus $^{65}$Zn chloride into the blood of two groups of 4 male Sprague-Dawley rats. The animals received a single oral dose of 5 $\mu$g $^{65}$Zn either as $^{65}$ZnCl$_2$ or $^{65}$Zn bisglycinate under light anesthesia following a 24-hour fast. Blood was taken from each animal by suborbital bleeding at specific intervals for 4 hours post dosing. Blood samples were assayed for $^{65}$Zn.

The results indicated that the rates of absorption of both sources of zinc are rapid. Increases in plasma levels occurred within 30 minutes. The major difference between the two sources however, was that the $^{65}$Zn bisglycinate yielded 30% higher blood levels, indicating an increased level of absorption (Peck and Graff, 1973).

The same authors carried out an *in vivo* study whereby two groups of 4 male Sprague-Dawley rats each received an intra-peritoneal dose of 5.0 $\mu$g of $^{65}$Zn as either $^{65}$Zn bisglycinate or as $^{65}$Zn chloride following a 24-hour fast. Four hours post dosing, each animal was sacrificed and a number of tissues were excised including thigh muscle tissue, left ventricle, liver, kidney and right cerebrum of brain. Each tissue sample was assayed for radioactivity. It was shown that the zinc deposition from $^{65}$Zn bisglycinate absorption was greater in muscle, kidney and brain (Peck and Graff, 1973).

In a study with dogs, a zinc amino acid chelate was evaluated to determine the bioavailability compared to zinc oxide with and without a calcium antagonist in the diet. Using a randomized block design, 4 adult beagles were first given a commercial control diet with zinc oxide for a period of 20 days. The animals were then given a diet supplemented with 50 mg/kg bw of Zn as oxide or amino acid chelate in the presence of or absence of 20 g/kg bw calcium. Zinc balance was determined using faecal collection for 5 days. Hair growth and hair zinc content was also determined. The authors found that the negative effect of calcium can be overcome through the use of zinc amino acid chelate, and that the zinc amino acid chelate treatment resulted in more hair and higher zinc content of the hair, suggesting higher bioavailability even in the face of dietary antagonisms (Lowe *et al*., 1994).

In a study with humans, the level of absorption of zinc from Zn amino acid chelate was measured in ten healthy adult males (mean age: 35 years). Participants underwent a stabilisation period of 45 days during which no nutritional supplements were given. The diet was monitored to ensure that the intake of essential nutrients was within the normal range. Blood and urine were then taken from each participant to determine baseline levels. Participants were then given 25 mg Zn amino acid chelate 3 times per day for a total of 75 mg/day for a period of 90 days. Samples were again taken from participants and the results compared to baseline.

The results showed a rise of over 40% (from 91.63 mg % to 131.25 mg %) in blood serum levels of zinc. In comparison, no rise in urinary zinc levels was detected (Ashmead, Unpublished report cited in the application dossier).

In another study with humans on the bioavailability of analogous amino acid chelates, the bioavailability of zinc from zinc histidine complexes as compared to zinc sulphate in 10 healthy volunteers was determined. Ingestion of zinc complexed with histidine at a ratio of 1:2 or 1:12 increased serum-zinc concentration 25% more than ingestion of zinc sulphate. Calculated uptake was 30 to 40% increased with zinc histidine compared with zinc sulphate. Urinary excretion was not different with any preparation. Application of 15 mg zinc as zinc histidine complex (1:2) gave an identical serum response as 45 mg zinc sulphate suggesting that the zinc histidine complex was better absorbed and subsequently, more bioavailable than zinc sulphate (Schölmerich *et al*., 1987).
6.1.1.3. Calcium bisglycinate

The petitioners indicate that no \textit{in vitro} studies have been conducted on calcium bisglycinate. In a study in humans to determine the absorption of calcium from calcium bisglycinate in comparison to other sources of calcium, a group of adult women (age from 20 to 40 years) with normal menstrual periods and no prior history of absorption disorders was selected. Most of the subjects were studied in the follicular phase of their menstrual cycles. The test subjects were given various forms of calcium (calcium bisglycinate, calcium citrate malate, calcium carbonate, tricalcium phosphate, calcium citrate, hydroxyapatite, calcium oxalate), which had been labeled with either $^{45}$Ca or $^{47}$Ca.

The data show that the percentage absorption of calcium from Ca-bisglycinate was 44.0 ± 10.4% which is higher than the absorption of calcium from the other Ca-sources which varied between 16.6 ± 9.0% and 24.2 ± 4.9% (Heaney, 1998, Unpublished report cited in the application dossier).

A study conducted by Greger \textit{et al.} (1987) showed similar bioavailability for a number of different calcium sources including milk, dibasic calcium phosphate, oyster shell, calcium carbonate, calcium lactate, calcium bisglycinate and dolomite.

6.1.1.4. Magnesium bisglycinate

The petitioners state that no \textit{in vitro} studies have been conducted on magnesium bisglycinate. There have been a number of studies with humans on the bioavailability of magnesium from magnesium amino acid chelate.

In a study to assess the absorption and retention characteristics of an oral dosage of magnesium amino acid chelate in human subjects, twenty-one employees (18 women and 3 men, ages ranging from 21 to 37 years) in a hospital in the USA were selected. Eleven subjects were given orally 360 mg/day of Mg-amino acid chelate and 10 subjects were given placebo capsules containing cellulose. The subjects were given an intravenous magnesium infusion at baseline and after 4 and 8 weeks of treatment and urinary magnesium and magnesium retention were measured.

The data show that following the magnesium infusion, urinary magnesium increased significantly (from 16.5±42.5 mg Mg/24h to 146.3±39.8 mg Mg/24h) in the test group but remained relatively constant in the placebo group. Similarly, the amount of magnesium retained from the infusion decreased significantly in the test group but remained constant in the placebo group.

From this the authors concluded that, since in the test group more magnesium from the infusion was excreted and less was retained, the data demonstrated that (i) the oral Mg-amino acid chelate was absorbed, and that (ii) the Mg-amino acid chelate was taken up by body tissues, thus reducing the need for magnesium from the infusion (Yang \textit{et al.}, 1989, Unpublished report cited in the application dossier).

6.1.1.5. Chromium glycinate nicotinate chelate

According to the petitioner there are no specific \textit{in vitro} studies currently available for chromium glycinate nicotinate chelate.

In an animal study, designed to determine the absorption of chromium from a chromium amino acid chelate (composition not specified by the petitioner in the application) in comparison to the absorption of chromium from inorganic chromium (III) chloride, two groups of rats (not
further specified) were slightly anesthetised and then intragastrically intubated with equal amounts of chromium as either $^{51}$CrCl$_3$ or the $^{51}$Cr-amino acid chelate. Blood was drawn at 1 hour intervals for 3 hours and equal volumes (100 µl) were measured for corrected disintegration counts per minute.

Data show that the absorption of chromium nearly doubled when supplied as chromium amino acid chelate, in comparison to inorganic chromic (III) chloride (Graff 1992, Unpublished report cited in the application dossier).

No direct data from studies with humans regarding the absorption of chromium are currently available for chromium glycinate nicotinate chelate. However, based on data obtained with regard to ferrous bisglycinate (EFSA, 2006), the petitioner anticipates that chromium from foods fortified with any chromium fortificant form will be more readily available than chromium from unfortified foods. In addition, chromium as a fortificant in the form of a chromium amino acid chelate will be no less available than chromium from inorganic forms.

A review article by Lukaski (1999) summarised two articles on the absorption of chromium. Lukaski stated that amino acids when chelating the dietary chromium prevent precipitation within the alkaline milieu of the small intestine. Similarly, nicotinic acid when administered with trivalent chromium will enhance absorption. In a radio-isotope study, it was found that $^{51}$Cr as nicotinate had significantly greater short-term retention (1-12 h post-gavage) in muscle, liver, kidney, blood and urine compared to the chromium chloride or chromium picolinate. In another study summarised by Lukaski, it was found that Cr nicotinate promoted Cr accumulation in the kidney and that nicotinate, like picolinate and acetate, increased Cr incorporation into the liver.

6.2 Toxicological data

The toxicity of the cations copper, zinc, calcium, magnesium and chromium has already been evaluated, and Tolerable Upper Intake Levels have been established (SCF, 1990; SCF, 2001; SCF, 2003d; EVM, 2003). Also nicotinic acid and nicotinamide have been evaluated and ULs have been derived (SCF, 2002).

As regards glycine, the SCF reviewed the nutritional, biochemical and toxicological information on glycine and concluded that, if used at levels corresponding to good manufacturing practice, no nutritional or toxicological hazards arise to man (SCF, 1990).

6.2.1. Subchronic toxicity

Presently, there are no specific studies on the subchronic toxicity of the bisglycinates of copper, zinc, calcium, magnesium or chromium (III). However, due to the similarity in chemical structure between these bisglycinates and ferrous bisglycinate, the petitioner anticipates that the bisglycinates under consideration in this opinion will exhibit similar subchronic toxicological characteristics as their ferrous bisglycinate counterpart. The Panel agrees that these studies can be used to assess the subchronic toxicity of the glycines. These characteristics have been fully described in the EFSA opinion on ferrous bisglycinate in 2006 (EFSA, 2006). In the study described in the ferrous bisglycinate opinion, no rats subjected to a 13-week study with treatments corresponding to 0, 100, 250, and 500 mg ferrous bisglycinate/kg bw/day died. Histopathological examination revealed no biologically or statistically significant, dose-dependent, macroscopic or microscopic findings that could be attributed to the treatment. Non-linear increases in mean hepatic non-haem iron concentrations indicated the existence of a physiological control on the absorption and distribution of the iron bisglycinate. Jeppsen and Borzelleca (1999) and Mandella (2000) reported a NOAEL of 500
mg/kg bw/day for ferrous bisglycinate in rats (the highest dose tested), corresponding to approximately 100 mg iron/kg bw/day and to approximately 400 mg glycinate/kg bw/day.

### 6.2.2. Genotoxicity

Genetic toxicity studies have not been conducted on calcium bisglycinate or magnesium bisglycinate.

The SCF makes reference to some *in vitro* and *in vivo* genotoxicity tests on other forms of zinc that have shown positive findings at elevated dosages, however, the SCF concluded that the weight of evidence from these studies did not indicate biologically relevant genotoxicity (SCF, 2003c).

The SCF in 2003, concluded that although chromium (III) compounds may bind to DNA and produce DNA-protein cross-links under certain circumstances they generally they did not produce gene mutations, sister chromatid exchanges or cell transformation in cultured mammalian cells. Weak clastogenic effects have been observed in some mammalian *in vitro* systems at relatively high and cytotoxic concentrations. No induction of genetic damage or micronuclei has been observed in experimental animals (SCF, 2003e). Therefore even though *in vitro* data show that Cr(III) has the potential to react with DNA and to cause DNA damage in cell culture systems, the available *in vivo* evidence suggests that genotoxic effects are not expected to occur in humans or animals exposed to nutritional or recommended supplemental levels of Cr(III) (Eastmond *et al*., 2008).

### 6.2.3 Longer-term feeding studies

The petitioner provided the results of two sets of longer-term feeding studies for the cations, copper, magnesium and zinc (Jeppsen, 1987; Jeppsen, 1990). The studies were carried out with production pigs (sows) that received feed rations containing amino acid chelates of the above mentioned cations, derived from hydrolysed soy protein. The Panel noted that, although this hydrolysate contained approximately 6% glycine, the resultant chelates were not characterised and are not directly equivalent to the chelates covered by this opinion. The dietary metal amino acid chelates were provided as extra supplementation and were not formulated to meet all of the nutritional needs of the pig. Metals in various other natural and non-chelated forms were already present in the dietary rations.

The first set of studies (Jeppsen 1987) were performed on a test farm where the animals had been administered the respective metal-amino acid chelates over the course of several years. They are considered by the petitioner as multigenerational studies representative for various filial generations of sows. The second set of studies (Jeppsen 1990) was conducted to assure that there was no toxicity due to the ingestion of the chelates by sows near the end of their reproductive lifetime.

The results of these studies showed that the respective metal-chelates were devoid of cumulative teratogenic effects and chronic morbidity, based both on practical observations and on observations at the macroscopic and microscopic level (Jeppsen, 1987). There were no significant differences in the gross examinations between the test and control group of sows and no histopathological tissue alterations were observed which could be attributed to metal-amino acid chelate. Haematological examinations likewise did not reveal any abnormalities related to administration of the test product (Jeppsen, 1990).

In a more recent study with pigs by Jeppsen (2005), magnesium amino acid chelate was administered as a dietary supplement to the sows throughout their life spans. The cumulative ingestion of magnesium per individual sow between the start of the study and its age at
sacrifice (range from approximately 38 to 52.5 months) varied between 93.7 g and 124.9 g. In comparison with control sows of similar age and parity, there were no observable gross or microscopic findings attributable to administration of the test product.

There are no specific chronic toxicity or carcinogenicity studies available on the individual metal bisglycinates.

There are also no specific chronic toxicity or carcinogenicity studies available on chromium glycinate nicotinate.

6.2.4 Reproductive and Developmental Toxicity

Reproductive toxicity studies in laboratory animals have not been conducted with copper amino acid chelates, zinc amino acid chelates, calcium amino acid chelates and magnesium amino acid chelates. However, in the longer term toxicity studies described above where sows received dietary supplementation with Cu-amino acid chelate throughout a period covering multiple litters, no adverse effects on reproduction or on the resulting offspring were observed.

Discussion

The bisglycinates considered in this opinion consist of a bivalent metal ion, namely Cu\(^{+2}\), Zn\(^{+2}\), Ca\(^{+2}\), and Mg\(^{+2}\), linked to two molecules of glycine. The metal is bound to the carboxyl group and to the \(\alpha\)-amino group of glycine with coordinate covalent bonds to form two heterocyclic rings. This 1:2 metal to ligand ratio restricts reaction with dietary inhibitors of the metal absorption and does not participate in oxidation reactions.

No specific use levels for the mineral bisglycinates under consideration in this opinion have been given. However, based on the information provided by the petitioner, under the conditions of intended use, the daily intake would not exceed those levels anticipated through existing supplementation of the listed minerals and would be similar to other forms of copper, zinc, calcium and magnesium that are already approved for use in foods in the EU.

Regarding the bioavailability of the different cations from their sources, data are provided showing that the minerals are bioavailable after oral administration.

No genetic toxicity studies have been conducted on the compounds considered in this opinion. However the Panel has no concern on the genotoxicity of glycine and nicotinic acid, nor on any of the metal cations under the expected conditions of use.

Due to the similarity in chemical structure between the metal glycinates considered in the present application and ferrous bisglycinate it is anticipated that the glycine part of these glycinates will exhibit similar toxicological characteristics as their ferrous bisglycinate counterpart, the safety of which was already evaluated and accepted by the AFC Panel in 2006. The Panel agrees that the subchronic studies on ferrous bisglycinate can be used to assess the subchronic toxicity of the glycinates. From the studies a NOAEL of 500 mg/kg bw/day for ferrous bisglycinate in rats (the highest dose tested) was derived, corresponding to approximately 400 mg glycinate/kg bw/day.

\(\text{In vitro}\) data show that Cr(III) has the potential to react with DNA and to cause DNA damage in cell culture systems, however, data from \(\text{in vivo}\) studies suggest that genotoxic effects are not expected to occur in humans or animals exposed to nutritional or recommended supplemental levels of Cr(III).

Specific chronic toxicity or carcinogenicity studies are not available.
Specific reproductive toxicity and developmental toxicity studies on the bisglycinates are also not available. However, in the longer-term feeding studies with livestock (female pigs) receiving dietary supplementation with mineral glycinites throughout a period covering multiple litters, no adverse effects on reproduction or on the resulting offspring were observed.

The Panel noted that these longer-term feeding studies are of limited value for the assessment of either chronic toxicity or carcinogenicity of the chelates, due to the relatively short duration of the studies relative to the life span of the pig and the small numbers of animals used in the studies.

A conservative estimate of the dietary exposure was made based on a hypothetical intake from all sources (PARNUTS, food supplements and foods intended for the general population) at the tolerable upper intake levels for copper (5 mg/day), zinc (25 mg/day), calcium (2500 mg/day) and magnesium (250 mg/day). Assuming that the mineral amino acid chelates concerned in this opinion would entirely be ingested in the bisglycinate form the equivalent exposure to glycine would be around 12 mg glycine/day for copper bisglycinate, 57 mg glycine/day for zinc bisglycinate, 9239 mg glycine/day for calcium bisglycinate and 1523 mg glycine/day for magnesium bisglycinate. The Panel noted that this estimated exposure is lower than the NOAEL of 400 mg glycinate/kg bw/day, the highest dose tested.

An intake of 1 mg of chromium under the form of chromium glycinate nicotinate would result in an exposure to approximately 3.3 mg nicotinic acid/day and 2.2 mg glycine/day. The Panel considered that such levels are not of safety concern.

In addition the normal (mean) intake of glycine in proteins from both food of animal origin (beef, pork, poultry, game, fish; glycine present at an estimated level of 1%), and vegetable origin (soya shoots, soya desserts, tofu, soya drinks, soya sauce, canola oil; glycine present at an estimated level of 6%) was calculated to be about 26 mg/kg bw/day for adults (>15 years) and to about 43 mg/kg bw/day for children (< 15 years).

**CONCLUSION**

The present opinion deals only with the safety of bisglycinate chelates of copper, zinc, calcium, magnesium, and of glycinate nicotinate as sources of the nutrient cations of respectively copper, zinc, calcium, magnesium and chromium and with the bioavailability of the nutrient cations from these sources. The safety of the nutrient cations themselves (copper, chromium, zinc, calcium and magnesium), in terms of amounts that may be consumed, is outside the remit of this Panel.

The Panel concludes that the use of copper bisglycinate chelate as a source for copper added for nutritional purposes to food supplements, and of calcium bisglycinate chelate and magnesium bisglycinate chelate as sources for respectively calcium and magnesium added for nutritional purposes to foods for particular nutritional uses and food supplements, and of zinc bisglycinate chelate when used as a source for zinc in foods intended for the general population (including food supplements) and foods for particular nutritional uses, is not of safety concern.

As regards chromium glycinate nicotinate complex, due to lack of information on the specific identity of its components, the Panel is unable to reach a conclusion on the safety of this source and on the bioavailability of chromium from this source.
DOCUMENTATION PROVIDED TO EFSA

1. Application for the approval of Copper bisglycinate (amino acid) chelate as a source for copper for use in the manufacture of foods, July 13, 2006; revised October 15, 2007. Submitted by Albion Laboratories, Clearfield, Utah, USA.

2. Application for the approval of Chromium glycinate nicotinate hydrochloride as a source for chromium for use in the manufacture of food supplements, July 13, 2006; revised October 15, 2007. Submitted by Albion Laboratories, Clearfield, Utah, USA.

3. Application for the approval of Zinc bisglycinate (amino acid) chelate as a source for zinc for use in the manufacture of foods, July 13, 2006; revised October 15, 2007. Submitted by Albion Laboratories, Clearfield, Utah, USA.

4. Application for the approval of Calcium bisglycinate (amino acid) chelate as a source for calcium for use in the manufacture of foods, July 13, 2006; Submitted by Albion Laboratories, Clearfield, Utah, USA.

5. Application for the approval of Magnesium bisglycinate (amino acid) chelate as a source for magnesium for use in the manufacture of foods, July 13, 2006; Submitted by Albion Laboratories, Clearfield, Utah, USA.


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Opinion on certain bisglycinates as sources of copper, zinc, calcium, magnesium and bisglycinate nicotinate as source of chromium


Opinion on certain bisglycinates as sources of copper, zinc, calcium, magnesium and bisglycinate nicotinate as source of chromium


### Glossary / Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AFC</td>
<td>Scientific Panel on food additives, flavourings, processing aids and materials in contact with food.</td>
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<tr>
<td>ADI</td>
<td>Acceptable Daily Intake</td>
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<tr>
<td>bw</td>
<td>Body weight</td>
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<tr>
<td>CAS</td>
<td>Chemical Abstract Service</td>
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<tr>
<td>DSHEA</td>
<td>Dietary Supplement Health and Education Act</td>
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<tr>
<td>EVM</td>
<td>Expert Group on Vitamins and Minerals</td>
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<tr>
<td>NOAEL</td>
<td>No Observed Adverse Effect Level</td>
</tr>
<tr>
<td>PARNUTS</td>
<td>Foods for Particular Nutritional Uses</td>
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<tr>
<td>SCF</td>
<td>Scientific Committee on Food</td>
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<td>SOD</td>
<td>Superoxide Dismutase</td>
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