

SCIENTIFIC OPINION

Copper(II) oxide as a source of copper added for nutritional purposes to food supplements¹

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

(Questions No EFSA-Q-2005-156, EFSA-Q-2006-219, EFSA-Q-2006-286, EFSA-Q-2006-287)

Adopted on 14 May 2009

PANEL MEMBERS

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SUMMARY

Following a request from the European Commission to the European Food Safety Authority, the Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to provide a scientific opinion on the safety of copper oxide added for nutritional purposes as a source of copper in food supplements and on the bioavailability of copper from this source.

The Panel notes, that even under the assumption that copper exposure from drinking water is unlikely to occur at the levels of the permitted maximum water copper concentration, exposure from foods at the 97.5th percentile is in the range of 1.2-4.2 mg copper/day, and that the exposure to copper from copper(II) oxide at the use levels proposed by the petitioners would lead to an additional copper exposure of 2-2.5 mg/day, resulting in total mean copper exposure of 3.6-4.7 mg/day for adults and 3.7-6.7 mg/day at the 97.5th percentile. For children the mean copper exposure is estimated to be at 3.4-3.6 mg/day and 4.1-4.9 mg/day at the 97.5th percentile assuming that children take the adult dose of the supplement. At the higher

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end this exposure may in some cases exceed the Tolerable Upper Intake Level of 5 mg/day established by the SCF. An additional exposure from water could increase the total exposure significantly.

Copper salts have moderate acute toxicity, with soluble salts being more toxic than insoluble ones. In short-term (2 weeks) repeated dose toxicity tests in rats and mice, copper salts are associated with adverse effects such as gastro-intestinal irritation and liver and kidney toxicity. Reported No-Observed-Adverse-Effect-Levels are in the range of 23-104 mg/kg bw/day copper, but kidney effects have been shown in male rats at levels as low as 10 mg/kg bw/day.

In a human study twenty subjects presented gastrointestinal disturbances at least once during the study, suffering diarrhoea (with or without abdominal pain and vomiting), and the other eleven subjects reported abdominal pain, nausea, or vomiting.

Copper(II) oxide shows lower bioavailability compared to other inorganic sources of copper(II), due to its low solubility. The Panel notes that copper from copper(II) oxide is expected to be bioavailable to some extent.

The Panel concludes that, provided that the Tolerable Upper Intake Level is not exceeded, the use of copper(II) oxide as a source of copper at the proposed use levels is not of safety concern.

Key words:

Food supplements, copper oxide, CAS Registry Number 1317-38-0

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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 copper oxide added for nutritional purposes to food supplements. The relevant Community legislative measure is:

- Directive 2002/46/EC of the European Parliament and of the Council on the approximation of the laws of the Member States relating to food supplements².

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 a scientific opinion, based on its consideration of the safety and bioavailability of copper oxide added for nutritional purposes in food supplements.

ACKNOWLEDGEMENTS

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² OJ L 183, 12.7.2002, p.51.

ASSESSMENT

1. Introduction

The present opinion deals only with the safety of copper(II) oxide as a particular source of copper and with the bioavailability of copper from copper(II) oxide. The safety of copper itself, in terms of amounts that may be consumed, is outside the remit of this Panel.

2. Technical data

2.1. Chemistry

Copper(II) oxide is a dark grey to black odourless amorphous powder, practically insoluble in ethanol and water, but soluble in weak and strong acids and slowly soluble in ammonia. Its chemical formula is CuO having a molecular weight of 79.54 g/mol and the CAS Registry Number is 1317-38-0.

Synonyms of copper oxide are copper(II) oxide, cupric oxide and black copper oxide.

2.2. Specifications

The chemical and microbial specifications of copper(II) oxide as proposed by the petitioners are listed in Table 1.

Table 1. **Chemical and microbial specifications for copper(II) oxide as proposed by the petitioners**

| | Technical Dossier 2005a | Technical Dossier 2005b | Technical Dossier 2005c | Technical Dossier 2005d |
|-----------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Chemical | | | | |
| Purity | > 99.9% | 99.0-101% | 99% | > 99% |
| Arsenic | < 3 mg/kg | | | < 3 mg/kg |
| Heavy metals (as Pb) | | | 10 mg/kg* | |
| Lead | < 5 mg/kg | < 50 mg/kg | 100 mg/kg | < 50 mg/kg |
| Cadmium | | | | < 20 mg/kg |
| Mercury | < 1 mg/kg | | | < 1 mg/kg |
| Iron | | < 50 mg/kg | 500 mg/kg | |
| Chloride | | < 50 mg/kg | 50 mg/kg | |
| Total sulphur (as sulphate) | | < 100 mg/kg | 200 mg/kg | |
| Total nitrogen | | < 20 mg/kg | 20 mg/kg | |
| Carbon | | < 1000 mg/kg | 100 mg/kg | |
| Potassium | | | 200 mg/kg | |
| Sodium | | | 500 mg/kg | |
| Microbial | | | | |
| Total plate count | | | 1000 cfu/g | |
| Yeast and mold | | | 100 cfu/g | |
| <i>E. coli</i> | | | negative | |
| <i>Salmonella</i> | | | negative | |

* The petitioner indicates a heavy metal concentration (as Pb) of 0.001 without any unit for this value; all other values provided in the chemical specification table of the dossiers are given in %, hence it was assumed that this is also true for heavy metals.

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).

2.3. Manufacturing process

The manufacturing process as described by one of the petitioners indicates the preparation by pyrolysis of copper(II) nitrate or copper(II) carbonate providing copper(II) oxide and either NO₂ (in case of copper(II) nitrate) or CO₂ (in case of copper(II) carbonate).

The preparation of copper(II) oxide by the addition of alkali hydroxide to a copper(II) salt solution and dehydration of the bulky blue slurry of copper(II) hydroxide to give copper(II) oxide is also mentioned.

2.4. Methods of analysis in food

Typical methods for the analysis of copper in food are Atomic Absorption Spectrometry (AAS) and Inductively Coupled Plasma spectrometry (ICP) following appropriate extraction and preparation of the samples. There is no specific method for copper(II) oxide as such, as indicated by the petitioner.

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

As there is no specific method for copper(II) oxide as such, the reaction and fate of copper(II) oxide in foods to which the source is added is monitored by the copper content of the product. The petitioners indicated that a change of the copper content cannot be expected and results are provided by one petitioner on the long-term stability of copper in a typical multi-vitamin and multi-mineral product (chewable tablet). In three different batches the copper content did not change after 36 months.

2.6. Case of need and proposed uses

Copper(II) oxide is to be used by food supplement manufacturers as an ingredient to tablets, caplets, capsules, chewable tablets, effervescent powders and liquids. The method of incorporation is determined by the different petitioners as appropriate for the particular type of finished product.

Copper(II) oxide is to be included in food supplements as a source of copper providing a maximum of 2 mg copper/day for adults, which is equivalent to 2.5 mg of copper(II) oxide. One petitioner indicated that a content of 2.5 mg copper, corresponding to 3 mg copper(II) oxide is also present on the market.

2.7. Information on existing authorisations and evaluations

In an earlier evaluation the Joint FAO/WHO Committee on Food Additives (JECFA) reaffirmed a previous tentative evaluation of a maximum daily load of 0.5 mg/kg body weight as a Provisional Maximal Tolerable Intake (PMTDI) for man from all sources, which amounts to 30 mg/day for a 60 kg person (JECFA, 1982). The Scientific Committee on Food (SCF) has established a Population Reference Intake (PRI) of 1.1 mg copper/day (SCF, 1993). The Tolerable Upper Intake Level (UL) for copper set by the SCF is 5 mg/day for adults (SCF, 2003), which would correspond to 6.34 mg/day of copper(II) oxide and 1-4 mg/day for children, depending on age. The UL takes into account copper intake from all food sources including supplements. Copper(II) oxide has not been evaluated for food use by either the SCF or JECFA, whereas copper as cupric sulphate has been evaluated several times by JECFA. Cupric sulphate was also evaluated by the SCF for food additive use as a colour stabilizer of canned green beans and cucumber salad (SCF, 1991). The SCF considered the possible intake from this use to be unlikely to contribute significantly to the total dietary intake of copper and would lie well below the PMTDI of 0.5 mg/kg bw calculated as Cu from all sources, established by JECFA. Therefore, the SCF considered the continued use of cupric sulphate for this purpose as toxicologically acceptable. Copper complexes of chlorophyll (E141i) and chlorophyllin (E141ii) are permitted food colours.

The International Programme on Chemical Safety (IPCS) has issued an extensive evaluation of copper and its salts (WHO, 1998).

2.8. Exposure

Food is the major source of copper intake; in particular, shellfish and organ meats (e.g. liver) provide rich sources of copper, but drinking water can make an important contribution in some circumstances. Copper concentrations in foods may vary widely between countries due to growing conditions, e.g. copper containing fertilizers and fungicides, and type of processing (WHO, 1998).

The SCF reported copper intakes from foods on average in the range from 1.1-2.2 mg/day and in the range from 1.2-4.2 mg/day at the 97.5th percentile (SCF, 2003) as shown in Table 2.

Table 2. **Summary information on copper intake and anticipated exposure to copper from copper(II) oxide**

| Nutrient: Copper | Intake (mg/day) | References |
|---|--|------------|
| Recommended intake/ adults | 1.1 | SCF, 1993 |
| Recommended intake/ children | 0.4-0.7 (up to 7 years) 0.8-1.0 (children older than 7 years and adolescents) | SCF, 1993 |
| Tolerable Upper Intake Level/ adults (excluding pregnant and lactating women) | 5 | SCF, 2003 |
| Tolerable Upper Intake Level/ children | 1 (1-3 years), 2 (4-6 years), 3 (7-10 years), 4 (11-17 years) | SCF, 2003 |

| | Average intake (mg/day) | High intake (97.5 th) (mg/day) | |
|--|-------------------------|--|------------------------------|
| Intake range from food in Europe for adults | 1.1-2.2 | 1.2-4.2 | SCF, 2003 |
| Intake range from food in Europe for children (3-17 years) | 0.9-1.1 | 1.6-2.4 | Leblanc <i>et al.</i> , 2005 |
| Amount of copper added as copper(II) oxide as indicated by the petitioner | 2.5 | | Technical dossier |
| Total anticipated exposure to copper from supplement and food intake ¹ for adults. | 3.6-4.7 | 3.7-6.7 | Calculation by Panel |
| Total anticipated exposure to copper from supplement and food intake ² for children (3-17 years). | 3.4-3.6 | 4.1-4.9 | Calculation by Panel |

¹ Calculation based on the proposed use level of 2.5 mg/day plus average dietary intake of 1.1-2.2 mg/day and high dietary intake of 1.2-4.2 mg/day for adults.

² Calculation based on the proposed use level of 2.5 mg/day plus average dietary intake of 0.9-1.1 mg/day and high dietary intake of 1.6-2.4 mg/day for children.

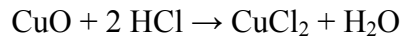
Other sources of copper exposure are emissions from mines, smelters and foundries, from the burning of coal for power generation and from municipal water incinerators. The contribution of airborne copper to total daily intake is considered as negligible. However, copper exposure can also result from copper plumbing, depending on the hardness, pH and quality of the water. Dissolved copper levels are higher in acidic waters, especially where pipe runs are long and water can stagnate. Thus, drinking water can make an important contribution to copper exposure in some circumstances. The Expert Group on Vitamins and Minerals (EVM) estimated the maximum copper exposure to be 11 mg/day with intake levels of 3 mg/day at the 97.5th percentile coming from foods, up to 2 mg/day from food supplements and up to 6 mg/day from drinking water (assuming 2 L/day consumption and the maximum permitted water copper concentration of 3 mg/L) (EVM, 2003). However EVM stated that there is no evidence that copper intakes from water (in the UK) present any risk to health, since in practice copper levels in UK drinking water are much lower and this level of exposure is unlikely to occur.

The Panel notes, that even under the assumption that copper exposure from drinking water is unlikely to occur at the levels of the permitted maximum water copper concentration, exposure from foods at the 97.5th percentile is in the range of 1.2-4.2 mg/day. Moreover, the exposure to copper from copper(II) oxide at the use levels proposed by the petitioners would lead to an additional copper exposure of 2-2.5 mg/day, resulting in total mean copper exposure of 3.6-4.7 mg/day for adults and 3.7-6.7 mg/day at the 97.5th percentile. For children the mean copper exposure is estimated to be at 3.4-3.6 mg/day and 4.1-4.9 mg/day at the 97.5th percentile assuming that children take the adult dose of the supplement. An additional exposure from water could increase the total exposure significantly.

3. Biological and toxicological data

3.1. Bioavailability

The bioavailability of copper from copper(II) oxide is mainly dependent on the solubilisation of the oxide in the gastrointestinal system. Copper(II) oxide dissolves in acids such as hydrochloric acid forming copper(II) chloride:



Copper(II) chloride is soluble in water (75.7 g/100 mL at 25° C) (Lide, 2009).

No specific data on the bioavailability of copper from copper(II) oxide were provided by the petitioners. One petitioner indicated, that it can be expected that, due to the acidic conditions in the stomach, copper(II) oxide will dissociate generating copper(II) ions and hydroxyl ions or water (depending on pH), rendering copper bioavailable from the source. However, the petitioner also stated that copper absorption is generally affected by a number of factors including the chemical form. Absorption of copper from various sources, mostly soluble salts such as copper sulphate, has been found to vary between 25-60% (JECFA, 1982), and the petitioner mentioned that it can be anticipated that the less soluble copper(II) salts will be in the lower end of that range.

In a series of human studies it has been convincingly demonstrated that the rate of copper absorption varies inversely with copper intake and can be as low as 12% with very high copper intakes. A theoretical maximum absorptive capacity of 63-67% has been estimated (Turnlund *et al.*, 1989).

The ingestion of copper as a mineral salt is relevant in humans only when taken as a nutritional supplement (Wapnir, 1998); in this situation, the potential of interactions with other mineral elements may have nutritional significance. The bioavailability of copper ranges between approximately 35% from normal diets and 60% from low copper diets (Winge and Mehra, 1990). Animal protein and fructose enhance copper absorption whilst vegetable protein, zinc, iron and calcium impede it (Hughes and Buttriss, 2000).

3.2. Toxicological data

The petitioner did not provide any specific data on the toxicity of copper(II) oxide but there are a lot of data on the toxicity of copper (ATSDR, 1990; EVM, 2003). Copper salts have moderate acute toxicity, with soluble salts being more toxic than insoluble ones. Consequently, the acute toxicity of copper(II) oxide is assumed to be rather low. Although the data are limited, rats appear to be more tolerant to acute copper toxicity than other species. In short-term (2 weeks) repeated dose toxicity tests in rats and mice, copper salts are associated with adverse effects such as gastro-intestinal irritation and liver and kidney toxicity. Reported No-Observed-Adverse-Effect-Levels (NOAELs) are in the range of 23-104 mg/kg bw/day copper, but kidney effects have been shown in male rats at levels as low as 10 mg/kg bw/day (ATSDR, 1990).

3.2.1. Animal toxicity data

There is a wide range of LD₅₀ values for different copper salts, and the more soluble copper salts tend to be more acutely toxic than those with lower solubility. In addition, although data are limited, rats appear to be less susceptible to the acute effects of copper than other animals (EVM, 2002).

3.2.2. Human toxicity data

Acute toxicity of copper in humans is rare. Copper ions (originated from any copper salts or oxide) have an irritant effect on mucosal membranes and daily intakes ranging from 2 to 32 mg in drinking water have been reported to cause symptoms of general gastric irritation (EPA, 1987). A study in Wisconsin also suggested that high levels of copper in the water supply may increase the rate of gastrointestinal upsets (Knobeloch *et al.*, 1998). A study on the acute gastrointestinal effects of drinking water containing graded levels of added copper (Pizarro *et al.*, 1999) showed that an average daily consumption of 1.64 litres of drinking water containing 3 mg/L ionised copper(II) was associated with nausea, abdominal pain or vomiting. A study to determine the tolerance of chronic exposure to copper in drinking water in infants aged 3-12 months (Olivares *et al.*, 1998) concluded that no acute or chronic adverse consequences were detected in the first year of life in infants by consuming water with a copper content of 2 mg/L.

In a human study both copper sulphate (a soluble compound) and copper(II) oxide (an insoluble compound) showed comparable effects, implying that the ionic copper present in the stomach is responsible for the induction of gastrointestinal manifestations. People with the condition of achlorhydria or elderly may be at increased risk for copper deficiency, as is the case for subjects consuming antacids, because copper absorption requires that the metal is in the ionized form.

Twenty subjects presented gastrointestinal disturbances at least once during the study, suffering diarrhoea (with or without abdominal pain and vomiting), and the other eleven subjects reported abdominal pain, nausea, or vomiting. No differences were found in incidence of abdominal pain, nausea, vomiting, and diarrhoea at different ratios of copper sulphate to copper(II) oxide. Both copper sulphate (a soluble compound) and copper(II) oxide (an insoluble compound) have comparable effects on the induction of gastrointestinal manifestations, implying similar levels of ionic copper were present in the stomach. Dose levels of copper(II) salts in this study were 5 mg/L drinking water and an average water consumption of 1.5/day (Pizarro, 2001).

4. Discussion

The Panel notes that the bioavailability of copper from copper(II) oxide is mainly dependent on the solubilisation of the oxide in the gastrointestinal system. It can be therefore expected that, due to the acidic conditions in the stomach, copper(II) oxide will dissociate into copper(II) ions and hydroxyl ions or water (depending on pH), rendering copper absorbable from the source in the lower end of the range that has been found for other inorganic sources of copper(II) of 25-60%.

The Panel notes, that even under the assumption that copper exposure from drinking water is unlikely to occur at the levels of the permitted maximum water copper concentration, exposure from foods at the 97.5th percentile is in the range of 1.2-4.2 mg copper/day, and that the exposure to copper from copper(II) oxide at the use levels proposed by the petitioners would lead to an additional copper exposure of 2-2.5 mg/day resulting in a worst case calculation for total copper exposure of 3.2-6.7 mg/day and that at the higher end this exposure may in some cases exceed the Tolerable Upper Intake Level of 5 mg/day established by the SCF.

Copper salts have moderate acute toxicity, with soluble salts being more toxic than insoluble ones. In short-term (2 weeks) repeated dose toxicity tests in rats and mice, copper salts are associated with adverse effects such as gastro-intestinal irritation and liver and kidney toxicity. Reported NOAELs are in the range of 23-104 mg/kg bw/day copper, but kidney effects have been shown in male rats at levels as low as 10 copper mg/kg bw/day.

Acute toxicity of copper in humans is rare. An average daily consumption of 1.64 litres of drinking water containing 3 mg/L ionised copper(II) was associated with nausea, abdominal pain or vomiting.

In a human study both copper sulphate (a soluble compound) and copper(II) oxide (an insoluble compound) showed comparable effects, implying that the ionic copper present in the stomach is responsible for the induction of gastrointestinal manifestations. Twenty subjects presented gastrointestinal disturbances at least once during the study, suffering diarrhoea (with or without abdominal pain and vomiting), and the other eleven subjects reported abdominal pain, nausea, or vomiting.

CONCLUSIONS

The present opinion deals with the safety of copper(II) oxide as a source for copper added for nutritional purposes to food supplements and with the bioavailability of copper from this source. The safety of copper itself, in terms of amounts that may be consumed, is outside the remit of this Panel.

Copper(II) oxide shows lower bioavailability compared to other inorganic sources of copper(II) due to its low solubility. However, the Panel notes that copper from copper(II) oxide is expected to be bioavailable to some extent.

The Panel concludes that, provided that the Tolerable Upper Intake Level is not exceeded, the use of copper(II) oxide as a source of copper at the proposed use levels is not of safety concern.

DOCUMENTATION PROVIDED TO EFSA

1. Technical dossier, 2005a. Dossier on Copper Oxide Proposed for the Addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. May 2005. Submitted by Heath Food Manufacturers Association.
2. Technical dossier, 2005b. Dossier for Safety Evaluation of Copper (II) Oxide. April 2005. Submitted by Béres Pharmaceuticals Ltd.
3. Technical dossier, 2005c. Dossier on Copper Oxide. Submitted by Kabco Pharmaceutical Ltd.
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GLOSSARY / ABBREVIATIONS

| | |
|-------|---|
| AAS | Atomic Absorption Spectrometry |
| ANS | Scientific Panel on Food Additives and Nutrient Sources added to Food |
| bw | body weight |
| CAS | Chemical Abstract Service |
| EC | European Commission |
| EFSA | European Food Safety Authority |
| EVM | Expert Group on Vitamins and Minerals |
| ICP | Inductively Coupled Plasma spectrometry |
| IPCS | International Programme on Chemical Safety |
| JECFA | Joint FAO/WHO Committee on Food Additives |
| NOAEL | No-Observed-Adverse-Effect Level |
| PMTDI | Provisional Maximal Tolerable Intake |
| PRI | Population Reference Intake |
| SCF | Scientific Committee on Food |
| UL | Tolerable Upper Intake Level |
| WHO | World Health Organisation |