European Food Safety Authority

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SCIENTIFIC OPINION

Assessment of the safety of cobalt(II) chloride hexahydrate added for nutritional purposes as a source of cobalt in food supplements and the bioavailability of cobalt from this source [1]

Statement of the Scientific Panel on Additives and Nutrient Sources added to Food (ANS)

(Question No EFSA-Q-2006-276)

Adopted on 28 April 2009

PANEL MEMBERS

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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 cobalt chloride hexahydrate added for nutritional purposes to food supplements. The relevant Community legislative measure is:

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

TERMS OF REFERENCE AS PROVIDED BY THE COMMISSION

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

[2] OJ L 183, 12.7.2002, p. 51.

STATEMENT

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

1. Summary of information provided on cobalt(II) chloride hexahydrate

The Panel notes from the documents provided by the petitioner that:

Cobalt is an essential trace element as a part of vitamin B12, which is necessary for folate and fatty acid metabolism.

The CAS registry number of cobalt(II) chloride hexahydrate is 7791-13-1. Synonyms are: cobalt chloride hexahydrate; cobalt dichloride hexahydrate; cobalt(II) chloride, hexahydrate; cobaltous chloride hexahydrate. It is a pure compound with a molecular formula $CoCl_2 \cdot 6(H_2O)$ and molecular weight of 237.93 g/mol. The structure of cobalt(II) chloride hexahydrate is reported to be $[CoCl_2(H_2O)_4] \cdot 2H_2O$.

Cobalt(II) chloride hexahydrate preparations contain not less than 97.0% and not more than 102.0% of cobalt(II) chloride hexahydrate. It is a violet (pink to red) odourless crystal. It is soluble in water (500 g/L at 20 °C) and in ethanol. The specifications are presented in the form of the technical sheet from the manufacturer (Merck KGaA). The manufacturing process is briefly described.

Because there is no method for the specific determination of cobalt chloride, it is the cobalt content that is determined in the food supplement. Quantitative determination of cobalt is performed by Inductively Coupled Plasma-Atomic Emission Spectrometry (ICP-AES). Cobalt(II) chloride hexahydrate is known to be a stable compound, therefore, effect of instability on the biological properties, including nutrient value, cannot be expected.

Cobalt(II) chloride hexahydrate is intended to be used in the form of hard gelatine capsules and of chewable, effervescent, film coated and uncoated, tablets. According to the petitioner typical amounts of cobalt(II) chloride hexahydrate to be used in food supplements range from 0.060-0.12 mg/day (which correspond to 0.015-0.030 mg cobalt/day).

A summary information on the bioavailability of cobalt from the source was also provided by the petitioner indicating that cobalt is bioavailable from the source.

From a Total Diet Study (TDS) conducted in the UK the average total daily intake of cobalt was estimated to be 0.012 mg/person.

There is no known authorisation of the source (cobalt(II) chloride hexahydrate).

2. Assessment

The bioavailability of cobalt from cobalt(II) chloride is reported to be higher compared to other inorganic cobalt compounds. In a human volunteer study, gastrointestinal uptake of the soluble cobalt compound, cobalt(II) chloride, was considerably greater than the uptake of the insoluble cobalt oxide; in females the amount absorbed may be three times higher than in males (Christiansen *et al.*, 1993). Absorption is also influenced by nutritional factors: amino acids reduce absorption, since both amino acids and sulphydryl groups complex with cobalt ions, whereas iron deficiency increases cobalt absorption (Elinder and Friberg, 1986). Gastrointestinal absorption appears to be dose dependent; very small doses (in the order of a few µg/kg bw) are absorbed almost completely (Clayton and Clayton, 1981).

A number of toxicity data show that cobalt and cobalt compounds such as cobalt chloride and cobalt sulphate may produce adverse health effects (Criteria group for Swedish occupational standards, 2005; Lison, 2007) such as cardiovascular toxicity, and reprotoxicity, as well as oxidative stress (Hoet *et al*., 2002) with possible DNA alterations (Baldwin *et al*., 2004, Colognato *et al*., 2008) and potentiation of the reactivity of neutrophil-derived oxidants (Ramafi *et al.*, 2004).

In its 2006 evaluation, the IARC (2006) concluded that: "The results of genotoxicity assays with cobalt salts demonstrate clearly their mutagenic potential. Recent experimental studies have contributed to better delineate the molecular mechanisms involved in the genotoxic (and carcinogenic potential) of cobalt ions. These mechanisms may conceivably apply both, to soluble cobalt compounds — for example, cobalt chloride or sulphate — and also to cobalt-metal or hard-metal particles, which are readily solubilised in biological media". The conclusion of the IARC was based on the results of numerous genotoxicity studies *in vitro* and *in vivo* (e.g. chromosomal aberrations were found in mice after oral administration of cobalt chloride (Palit *et al.*, 1991); DNA breakage was shown in human lymphocytes exposed *in vitro* to non cytotoxic cobalt(II) chloride concentrations (De Boeck *et al.*, 1998; Lison *et al.*, 2001). Cobalt(II) chloride hexahydrate is classified as a class 2B carcinogen by IARC.

Inhalation of cobalt chloride in rats and mice produced lung tumours, on the basis of which the EC has classified this substance as carcinogenic (Carc. Cat 2, R49[3])

On the basis of sufficient *in vivo* animal data on somatic cells, the EC has classified cobalt (II) chloride hexahydrate as mutagenic (Muta. Cat 3, R68[4]).

CONCLUSIONS

The Panel concludes that the bioavailability of cobalt from cobalt(II) chloride hexahydrate is higher than from other inorganic sources (i.e. cobalt oxide).

Given the toxicological profile of cobalt(II) chloride hexahydrate, including genotoxicity and carcinogenicity, the Panel concludes that the proposed uses of cobalt(II) chloride

[3] According to Directive 67/548/EEC the meaning of the risk phrase R 49 is : may cause cancer by inhalation

[4] According to Directive 67/548/EEC the meaning of the risk phrase R 68 is : possible risk of irreversible effects

hexahydrate added for nutritional purposes in food supplements as a source of cobalt are of safety concern.

Key words:

Food supplements, cobalt chloride hexahydrate, CAS number 7791-13-1.

DOCUMENTATION PROVIDED TO EFSA

Dossier on cobalt chloride hexahydrate proposed for addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. 2005. Submitted by Béres Pharmaceuticals Co. Ltd. Budapest, HUNGARY

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GLOSSARY / ABBREVIATIONS

ANS	Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS)
CAS	Chemical Abstracts Service
EC	European Commission
EFSA	European Food Safety Authority
IARC	International Agency for Research on Cancer
ICP-AES	Inductively Coupled Plasma Atomic Emission Spectrometry
TDS	Total Diet Study