European Food Safety Authority

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SCIENTIFIC OPINION

Chromium nitrate as a source of chromium added for nutritional purposes to food supplements [1]

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

(Question No EFSA-Q-2005-216)

Adopted on 2 June 2009

PANEL MEMBERS

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SUMMARY

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

The present opinion deals only with the safety of a particular source of chromium, chromium(III) nitrate, intended to be used in food supplements and with the bioavailability of chromium from this source. The safety of chromium itself, in terms of the amounts that may be consumed, is outside the remit of this Panel.

In the adult population (over 18 years old), assuming mean and 97.5th percentile European dietary chromium(III) intakes in the ranges of 60–160 µg/day and 126-170 µg/day, respectively, consumption of food supplements containing 500 µg chromium(III)/day (the highest use level proposed by the petitioner) would result in a total anticipated daily chromium intake, from food and food supplements, between 560 and 660 µg

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chromium(III)/day at the average level of dietary exposure and between 626 and 670 µg/day at the high level of dietary exposure, if no other food supplements containing chromium(III) were taken.

In children aged 3 to 17 years old, assuming mean and 97.5th percentile dietary chromium(III) intakes in the ranges of 63–69 µg/day and 107-119 µg/day, respectively, consumption of food supplements containing 500 µg chromium(III)/day (the highest use level proposed by the petitioner) would result in a total anticipated daily chromium intake, from food and food supplements, between 563 and 569 µg chromium(III)/day at the average level of dietary exposure and between 607 and 619 µg/day at the high level of dietary exposure, if no other food supplements containing chromium(III) were taken.

No bioavailability data specific for chromium(III) nitrate were presented but, the petitioner states that being highly soluble, chromium(III) nitrate fully dissociates into its two components (nitrate and chromium(III)) in the stomach and therefore it should be absorbed in the same manner as chromium(III) chloride. In the absence of specific supporting data, this statement cannot be evaluated but the Panel considers that the bioavailability of chromium(III) from chromium(III) nitrate could be expected to be similar to that for other inorganic soluble chromium salts. In any case, this absorption is low (0.5-2%).

If, as stated by the petitioner, the compound readily dissociates in the stomach, the Panel considers that the safety of the compound must be assessed regarding its two components: nitrate and chromium(III).

Nitrates have been assessed by the Scientific Committee on Food (SCF), EFSA and the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the estimated dietary exposure to nitrate is about 157 mg/day. Given the proposed uses for chromium(III) nitrate as a food supplement, a daily intake of 0.5 mg of chromium(III) will be associated with a daily intake of approximately 1.8 mg of nitrate. The Acceptable Daily Intake (ADI) for nitrate is 3.7 mg/kg bw/day, equivalent to 222 mg/day for a 60 kg adult. On the basis of the information available in the dossier, given the proposed use levels presented by the petitioner and the resulting exposure to nitrate, the Panel concludes that the amount of nitrate that would be consumed as a result of the proposed uses of chromium(III) nitrate as a source of chromium would not be of safety concern.

The toxicity of chromium compounds has been evaluated by various authorities including the SCF, the UK Expert group on Vitamin and Minerals (EVM), the US Food and Nutrition Board (FNB) and the World Health Organization (WHO).

The SCF has issued an opinion on the Tolerable Upper Intake Levels (ULs) of trivalent chromium (chromium(III)) and concluded that limited data from studies on subchronic, chronic and reproductive toxicity on soluble trivalent chromium salts and the available human data do not give clear information on the dose-response relationships and therefore a UL could not be derived.

The US FNB concluded that data from animal and human studies are insufficient to establish a UL for soluble trivalent chromium salts.

The EVM also concluded that overall there are insufficient data from human and animal studies to derive a safe upper level for chromium. However, in the EVM opinion it was indicated that a total daily intake of about 0.15 mg chromium(III)/kg bw/day (or 10 mg/person) was expected to be without adverse health effects.

The WHO considered that supplementation of chromium in adults should not exceed 250 μg/day.

Information on the toxicity of chromium(III) is limited but given the available data the Panel concludes that the use of chromium(III) nitrate as a source of chromium(III) in food supplements would not be of safety concern provided that the level for supplementation of 250 μg chromium/day recommended by the WHO is not exceeded.

In addition, the Panel notes that recent reviews and evaluations of chromium(III) point at conflicting outcomes of genotoxicity assays and report diverging views and conclusions on the consequences of this genotoxicity issue for the ultimate safety assessment of chromium(III). The Panel notes that additional relevant in vivo studies have shown that exposure to chromium(III) chloride and chromium(III) nitrate induced DNA deletions in mice and yeast respectively and that it was recently reported that occupational exposure to chromium(III) can lead to DNA damage to human peripheral lymphocyte as evidenced by the Comet assay. The Panel is aware that given this situation the safety of chromium(III) might need to be re-evaluated in light of these recent reviews and evaluations.

Key words:

Chromium nitrate, CAS Registry Number 13548-38-4 (anhydrous); CAS Registry Number 7789-02-8 (nonahydrate), food supplement

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BACKGROUND

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 chromium nitrate 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

TERMS OF REFERENCE

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 chromium nitrate added for nutritional purposes in food supplements.

ACKNOWLEDGEMENTS

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ASSESSMENT

1. Introduction

The present opinion deals only with the safety of a particular source of chromium, chromium(III) nitrate, intended to be used in food supplements and with the bioavailability of the chromium from this source. The safety of chromium itself, in terms of the amounts that may be consumed, is outside the remit of this Panel.

2. Technical data

2.1. Chemistry

Anhydrous chromium nitrate is a chemical with the molecular formula $Cr(NO_3)_3$, a molecular mass of 238.01 g/mol and the CAS Registry Number 13548-38-4. The nonahydrate form ($Cr(NO_3)_3 \cdot 9H_20$) has a molecular mass of 400.21 g/mol and a CAS Registry Number 7789-02-8.

Synonyms proposed by the petitioner are chromic nitrate nonahydrate, chromium(III) nitrate, chromium trinitrate.

2.2. Specifications

Chromium nitrate is described by the petitioner as a pale green powder and the nonahydrate form as a violet crystalline powder, which is freely soluble in water.

The petitioner indicates that the purity is not less than 99.9% on the anhydrous basis. The limits for impurities are as follow: arsenic $\leq$ 3 mg/kg; lead $\leq$ 5 mg/kg; mercury $\leq$ 1 mg/kg.

The Panel notes that according to Commission Regulation (EC) No 629/2008 (EC, 2008) the maximum levels of lead, mercury and cadmium in food supplements as sold should be 3 mg/kg, 0.1 mg/kg and 1 mg/kg, respectively.

2.3. Manufacturing process

Chromium nitrate is obtained by dissolving chromium hydroxide in nitric acid and crystallising out the chromium nitrate nonahydrate.

2.4. Methods of analysis in food

The petitioner indicated that chromium nitrate may be identified by infrared (IR) spectrometry and that the content of chromium can be analysed by Atomic Absorption Spectroscopy (AAS) and Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES) following an appropriate extraction and preparation of the samples.

No information was provided for the determination of nitrate.

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

The petitioner indicated that the compound was stable in food. However, no supporting data have been provided.

2.6. Case of need and proposed uses

The petitioner proposed to use chromium nitrate as a source of chromium in food supplements to provide 20–500 µg chromium/day for adults (corresponding to 70-1789 µg nitrate/day). The petitioner indicated that chromium nitrate is included in food supplement products to provide 20 to 500 µg chromium/day for adults and typically provides 100-200 µg in one tablet to be taken daily.

2.7. Information on existing authorisations and evaluations

Nitrates have been assessed by the SCF (1992, 1997), JECFA (2003a,b) and EFSA (2008). The Acceptable Daily Intake (ADI) for nitrate is 3.7 mg/kg bw/day (SCF, 1992), equivalent to 222 mg nitrate/day for a 60 kg adult.

Chromium(III) chloride and chromium(III) sulphate are included in Annex II of the Food Supplements Directive 2002/46/EC (EC, 2002) as approved sources of chromium and also within Annex Category 2 of Directive 2001/15/EC (EC, 2001) as substances that may be added for specific nutritional purposes to food for particular nutritional uses (PARNUTS).

The SCF has previously given an opinion on the Tolerable Upper Intake Level (UL) of chromium(III) (SCF, 2003). The SCF considered that the data from studies on subchronic, chronic and reproductive toxicity in experimental animals of soluble trivalent chromium salts and the available human data did not provide clear information on the dose-response relationships, and therefore the SCF was not able to derive a UL for chromium. The UK EVM (2002, 2003) similarly concluded that overall there were insufficient data from human and animal studies to derive a safe upper level for chromium. However, in the EVM opinion it was indicated that a total daily intake of about 150 µg chromium(III)/kg bw/day (approximately 10 mg/day for a 70 kg person) would be expected to be without adverse health effects (EVM, 2003). The US FNB also concluded that the data from animal and human studies are insufficient to establish an UL for soluble chromium(III) salts (FNB, 2001), while the WHO considered that supplementation of chromium should not exceed 250 µg/day (WHO, 1996). The Societies for Nutrition of Germany (DGE), Austria (ÖGE) and Switzerland (SGE), jointly established an ADI of 30-100 µg chromium/day for adults (D-A-CH, 2000).

The Institute of Medicine (IOM) reported that there is not sufficient evidence to set an Estimated Average Requirement (EAR) for chromium (IOM, 2001). Therefore, based on estimated mean intakes, Adequate Intakes (AIs) were set at 35 and 25 µg/day for young men and women, respectively.

2.8. Exposure

Chromium

The Panel noted that chromium is a trace element and that in its trivalent form, it is ubiquitous in the environment and naturally present in meat, grains lentils and spices.

Currently, chromium(III) is used in food supplements in a number of countries in the European Union. Exposure to chromium(III) also commonly occurs via food, with the highest levels being found in meat and meat products, oils and fats, breads and cereals, fish, pulses and spices (SCF, 2003; EVM, 2003).

The SCF report provides information on average chromium dietary intakes, ranging from 60 to 160 µg/day in adults in some European countries (SCF, 2003). The 97.5th percentile dietary intake values of chromium were reported to range from 126 to 170 µg/day (Leblanc *et al.*, 2005; SCF, 2003). Data from the French Total Diet Study provided average intakes of chromium of 63 µg/day for children aged 3-10 years old and 69 µg/day for 11-17 years old, and high percentile intakes of 107 µg/day for 3-10 years old and 119 µg/day for 11-17 years old.

In the adult population (over 18 years old), assuming mean and 97.5th percentile European dietary chromium(III) intake in the ranges of 60–160 µg/day and 126-170 µg/day, respectively, consumption of food supplements containing 500 µg chromium(III)/day (the highest use level proposed by the petitioner) would result in a total anticipated daily chromium intake, from food and food supplements, between 560 and 660 µg chromium(III)/day at the average level of dietary exposure and between 626 and 670 µg/day at the high level of dietary exposure, if no other food supplements containing chromium(III) were taken (Table 1).

In children aged 3 to 17 years old, assuming mean and 97.5th percentile dietary chromium(III) intakes in the range of 63–69 µg/day and 107-119 µg/day, respectively, consumption of food supplements containing 500 µg chromium(III)/day (the highest use level proposed by the petitioner) would result in a total anticipated daily chromium intake, from food and food supplements, between 563 and 569 µg chromium(III)/day at the average level of dietary exposure and between 607 and 619 µg/day at the high level of dietary exposure, if no other food supplements containing chromium(III) were taken (Table 1).

Table 1. **Summary information on chromium intake and anticipated potential exposure to chromium from chromium(III) nitrate**.

Nutrient: Chromium	Amount (µg/day)	Average intake (µg/day)	High intake (µg/day)	References
Recommended Daily Intake	30 to 100 for adults			D-A-CH, 2000
Maximum level of supplementation	250			WHO, 1996
Intake range from food in Europe for adults		60-160	126-170	SCF, 2003 Leblanc *et al.*, 2005
Intake range from food in Europe for children (3-17 years old)		63-69	107-119	Leblanc *et al.*, 2005

Daily amount of chromium(III) added to food supplements from chromium nitrate as indicated by petitioner	500			Technical dossier 2005
Source: Chromium nitrate				
Total anticipated exposure to chromium from food supplements and dietary intake for adults [1]		560-660	626-670	Calculation by the Panel
Total anticipated exposure to chromium from food supplements and dietary intake for children (3-17 years old)[2]		563-569	607-619	Calculation by the Panel

[1]calculation based on proposed use level of 500 µg/day plus average dietary intake of 60-160 µg/day and high dietary intake of 126-170 µg/day for adults.

[2]calculation based on proposed use level of 500 µg/day plus average dietary intake of 63-69 µg/day and high dietary intake of 107-119 µg/day for children.

Nitrate

Vegetables contain higher levels of nitrate than other foods and contribute the most to dietary nitrate exposure. Plants have different storage capacities for nitrate, with spinach and lettuce often containing more significant amounts, and rucola having the highest amounts (EFSA, 2008).

Given the proposed use for chromium nitrate as a food supplement, a daily intake of up to 0.5 mg of chromium results in an associated daily intake of approximately 1.8 mg of nitrate. An ADI for nitrate of 3.7 mg/kg bw/day, equivalent to 222 mg nitrate/day for a 60 kg adult and 114.7 mg/day in a 31 kg child was established by the SCF (SCF, 1992, 1997) and reconfirmed by JECFA (JECFA, 2003a,b) and EFSA (EFSA, 2008).

Reported average European dietary intakes of nitrates range from 55 mg/day in the adult Finnish population (Pentilà, 1990) to 190 mg/day in French adults (Menard *et al*., 2008). High percentile intake values for nitrates were reported from 113 mg/day in Danish adults (Petersen and Stoltze, 1999) and up to 198 mg/day in French adults (Menard *et al*., 2008). The average intakes for children have been reported to vary between 0.9 mg/day in Estonia (Reinik *et al*., 2005) and 62 mg/day in France (Menard *et al.*, 2008). High intake values for nitrates for children have only been reported in France and are equal to 151.9 mg/day (Menard *et al.,* 2008).

Assuming mean and high percentile European dietary nitrate intakes in the ranges of 55–190 µg/day and 113-198 µg/day, respectively, consumption of an additional food supplement containing 1.8 mg of nitrate (the maximum dose proposed by the petitioner) would result in a total daily nitrate intake between 56.8 and 191.8 mg nitrate/day in an adult at the average level and between 114.8 to 199.8 mg/day at the high level of dietary nitrate intake.

In children, assuming mean and high percentile dietary nitrate intakes in the ranges of 0.9 – 62 mg/day and 151.9 mg/day, respectively, consumption of an additional food supplement containing 1.8 mg nitrate/day (the maximum dose proposed by the petitioner) would result in a total daily nitrate intake between 2.7 and 63.8 mg nitrate/day at the average level and 153.7 mg/day at the high level of dietary nitrate intake

3. Biological and toxicological data

3.1. Bioavailability

No specific information on the bioavailability of chromium from chromium nitrate was provided by the petitioner. According to the petitioner, chromium(III) nitrate is highly soluble in water, fully dissociating in the stomach and chromium(III) is then absorbed in the same manner as from chromium(III) chloride.

Differences in chromium(III) bioavailability have been reported depending on the ionic form and/or the organic or the inorganic forms of chromium. In the intestine of black ducks, chromium was absorbed from saline solutions of chromium potassium sulphate ($KCr(SO_4)_2$) and chromium trioxide (CrO_3) at a rate of about 1.5 to 2.0 times greater than from solutions of chromium nitrate ($Cr(NO_3)$) and the organic salt, 2,4-pentanedione chromium ($Cr(C_5H_7O_3)_3$) (Eastin *et al.,* 1980). Using an *in vitro* model of the rat jejunum, very limited differences in the absorption of chromium(III) between the inorganic salts, chromium chloride and chromium nitrate, and the organic salt, chromium picolinate, have been reported, however the organic form penetrates the jejunum more efficiently than the inorganic salts (Gammelgaard *et al.*, 1999). Therefore the Panel considers that chromium from the nitrate and chloride salts should be absorbed in a similar way.

Intestinal absorption of chromium(III) is low (0.5-2%). The mechanism of absorption is still unclear but it appears to involve processes other than passive diffusion (EVM, 2003). Following absorption, trivalent chromium binds to plasma proteins such as transferrin and is transported to the liver, a process partly regulated by insulin (Clodfelder *et al*, 2001). In humans, chromium concentrates in the liver, spleen, soft tissue, and bone; a similar pattern is seen in rats with incorporation in the kidneys and testes in addition to the liver, spleen, brain, and bone (FNB, 2001; Tandon *et al.*, 1979). Mertz *et al*. (1965) proposed a three-compartment model with half-lives of 0.5, 5.9, and 83 days based on studies of radiolabelled chromium ($^{51}CrCl_3$) in rats. Urine is the main excretory route for absorbed chromium in both animals and humans, with small amounts also being excreted in perspiration and bile. Urinary chromium excretion reflects the dietary chromium intake in a dose-dependent manner (Kumpulainen, 1992; Uusitupa *et al.,* 1992).

Trivalent chromium potentiates insulin action and thereby influences carbohydrate, lipid and protein metabolism. Chromium binds to transferrin (Peterson, 1967), and interactions between iron and chromium are therefore possible, resulting in impairment of iron storage and metabolism.

3.2. Toxicological data

No specific data were provided by the petitioner about the toxicological profile of the source or of nitrate. The information provided by the petitioner referred only to the toxicity of trivalent chromium (EVM, 2003).

The toxicity of chromium compounds has been reviewed by several institutions (IPCS, 1988, 2006; WHO, 1996, 2009; EPA, 1998; IOM, 2001; EVM, 2003; SCF, 2003; IARC, 1990).

Nitrates have been assessed by the SCF (1992, 1997), JECFA (2003a,b) and EFSA (2008).

3.2.1. Human data on chromium:

No relevant data were provided by the petitioner on chromium(III) nitrate.

3.2.2. Animal studies on chromium

3.2.2.1. Acute toxicity

No information was provided by the petitioner on the acute toxicity of chromium(III) nitrate in animals.

3.2.2.2. Subchronic and chronic toxicity

As noted by the SCF (2003) and the EVM (2003) there are limited data from subchronic and chronic studies on the toxicity of soluble trivalent chromium salts. The available data provided by the petitioner were limited. Oral exposure to trivalent or hexavalent chromium compounds resulted in adverse intestinal, hepatic, renal, immunological, neurological developmental and reproductive effects. Trivalent chromium appears less toxic than hexavalent chromium (EVM, 2003) with chronic intakes of up to 750 mg/kg bw/day not being associated with adverse effects. Both forms of chromium have been reported to reduce fertility, foetal weight, and crown length and increase post-implantation in mice (EVM, 2003).

The SCF (2003) reports that chromium chloride given in drinking water at levels of 2000 or 5000 mg/L *ad libitum* for 12 weeks to Swiss mice reduced body weights (male only) and fertility. Significant changes in the weights of reproductive organs have also been noted (Elbetieha and Al Hamood, 1997). The SCF noted that Elbetieha and Al Hamood (1997) did not report the actual intake of chromium chloride but oral doses for chromium(III) of approximately 500 or 1250 mg/kg bw/day for females and 250 or 1250 mg/kg bw/day for males were estimated by the EVM (EVM, 2003). The SCF (2003) also reported that the weight of reproductive organs in male Sprague Dawley rats exposed to chromium(III) chloride in drinking water (1000 mg/L for 12 weeks, equivalent to about 50 mg chromium chloride/kg bw/day or about 16.5 mg chromium(III)/kg bw/day), was significantly reduced (Bataineh *et al.*, 1997).

In a 2-year study on rats and mice of both sexes, exposed (in feed) to chromium(III) picolinate monohydrate at very high concentrations (equivalent to 0, 10.7, 54.9 and 286.2 mg Cr(III)/kg bw/day), no effect on body weight and no significant adverse effects were reported (NTP, 2008; Stout *et al.*, 2009).

3.2.2.3. Genotoxicity

Levina and Lay (2008) discussed the chemical transformations of chromium(III) nutritional supplements in biological media, with implications for both beneficial and toxic actions of chromium(III) complexes, which are likely to arise from the same biochemical mechanisms, dependent on the concentrations of the reactive species. These species include: (i) partial hydrolysis products of chromium(III) nutritional supplements, which are capable of binding

to biological macromolecules and altering their functions; and (ii) highly reactive chromium(VI/V/IV) species and organic radicals, formed in reactions of chromium(III) with biological oxidants. Low concentrations of these species are likely to cause alterations in cell signalling (including enhancement of insulin signalling) through interactions with the active centers of regulatory enzymes in the cell membrane or in the cytoplasm, while higher concentrations are likely to produce genotoxic DNA lesions in the cell nucleus.

The Panel notes that recent reviews and evaluations of chromium(III) (Eastmond *et al.,* 2008; Levina and Lay, 2008) point at conflicting outcomes of genotoxicity assays and report diverging views and conclusions on the consequences of this genotoxicity issue for the ultimate safety assessment of chromium (III). The Panel notes that additional relevant *in vivo* studies have shown that exposure to chromium(III) chloride and chromium(III) nitrate induced DNA deletions in mice and yeast respectively (Kirpnick-Sobol *et al.*, 2006) and that it was recently reported that occupational exposure to chromium(III) can lead to DNA damage to human peripheral lymphocyte as evidenced by the Comet assay (Zhang *et al.*, 2008).

3.2.2.4. Carcinogenicity

According to the International Agency for Research on Cancer (IARC) "metallic chromium and chromium(III) compounds are not classifiable as to their carcinogenicity to humans" (Group 3) (IARC, 1990). In recent chronic toxicity and carcinogenicity studies, rats and mice (Stout *et al.,* 2009) were exposed for 2 years (in feed) to chromium(III) picolinate monohydrate at very high concentrations equivalent to 0, 10.7; 54.9 and 286.2 mg chromium(III)/kg bw/day. The data showed very little evidence of adverse effects; in male rats, there was equivocal evidence of carcinogenic activity based on increased preputial gland adenomas (only in the 54.9 mg chromium(III)/kg bw/day dose group). There was no evidence of carcinogenic activity in female rats or in male and female mice.

3.2.2.5. Toxicity of nitrate

Nitrates have been assessed by the SCF (1992, 1997), JECFA (2003a,b) and EFSA (2008). The ADI for nitrate is 3.7 mg/kg bw/day, equivalent to 222 mg nitrate/day for a 60 kg adult.

4. Discussion

The IOM (2001) reported that there is insufficient evidence to set an EAR for chromium. Therefore, based on estimated mean intakes, an AI was set at 35 µg/day and 25 µg/day for young men and women, respectively. The SCF report (2003) provides information on chromium(III) dietary intakes in some European countries which range from 60 µg/day in average to 170 µg/day at the 97.5th percentile. The petitioner indicated that chromium nitrate is included in food supplements to provide from 20 to 500 µg chromium(III)/day in adults and typical uses provide 100-200 µg in a single tablet to be taken daily. On the basis of these figures, consumption of food supplements containing 500 µg chromium(III)/day in addition to the dietary intake would result in a total daily intake of chromium(III) varying from 560 µg (at the average level of dietary exposure) up to 670 µg (at the high level of dietary exposure).

The Panel notes that the highest level of chromium supplementation proposed by the petitioner (500 µg/day) is above the level of 250 µg chromium/day considered by the WHO as a value for supplementation that should not be exceeded.

No data on the bioavailability of chromium from chromium nitrate were presented, but the petitioner states that chromium(III) nitrate being highly soluble, it fully dissociates in the stomach into its two components (nitrate and chromium(III)) and therefore chromium(III) from chromium(III) nitrate should be absorbed in the same manner as chromium from chromium(III) chloride. The Panel considers that the bioavailability of chromium from chromium nitrate could be expected to be similar to that from other inorganic soluble chromium salts. In any case, this absorption is low (0.5-2%).

If, as stated by the petitioner, the compound readily dissociates in the stomach, the Panel considers that the safety of the compound must be assessed regarding its two components: nitrate and chromium(III).

The Panel notes that nitrates have been assessed by the SCF (1992, 1997), JECFA (2003a,b) and EFSA (2008). The use of chromium nitrate to provide a daily intake of 250 µg of chromium(III) will be associated with a daily intake of approximately 0.9 mg of nitrate. The Panel noted that this amount of nitrate corresponds to 0.6% of the ADI (3.7 mg/kg bw/day) for a 60 kg adult (SCF, 1992)). The additional amount of nitrate coming from consumption of food supplements appears limited but yet not advisable in the context of a chemical which is one of the four priorities identified by the WHO (2007) and taking into account the risks and benefits (Bottex *et al*. 2008).

The Panel notes that recent reviews and evaluations of chromium(III) (Eastmond *et al.,* 2008; Levina and Lay, 2008) point at conflicting outcomes of genotoxicity assays and report diverging views and conclusions on the consequences of this genotoxicity issue for the ultimate safety assessment of chromium(III). The Panel notes that additional relevant *in vivo* studies have shown that exposure to chromium(III) chloride and chromium(III) nitrate induced DNA deletions in mice and yeast respectively (Kirpnick-Sobol *et al.*, 2006) and that it was recently reported that occupational exposure to chromium(III) can lead to DNA damage to human peripheral lymphocyte as evidenced by the Comet assay (Zhang *et al*., 2008). The Panel is aware that given this situation the safety of chromium(III) might need to be re-evaluated in light of these recent reviews and evaluations.

CONCLUSIONS

The present opinion deals only with the safety of chromium(III) nitrate as a source of chromium added for nutritional purposes to food supplements and with the bioavailability of chromium from this source.

In view of the petitioner's statement that chromium nitrate is highly soluble and fully dissociates in the stomach, the Panel considers that the safety of the chromium(III) nitrate must be assessed regarding its two components: nitrate and chromium(III).

The Panel concurs with the view of the SCF that overall, the bioavailability of chromium(III) is low and therefore the bioavailability of chromium from chromium(III) nitrate is low and likely to be similar to that of chromium from the diet (0.5-2%).

The Panel concludes that the use of chromium(III) nitrate as a source of chromium(III) in food supplements would not be of safety concern provided the level for supplementation of

250 µg chromium/day recommended by the WHO is not exceeded. This amount would result in an exposure to nitrate of approximately 0.9 mg of nitrate corresponding to 0.6% of the ADI for a 60 kg adult which is not of safety concern.

In addition, the Panel notes that recent reviews and evaluations of chromium(III) point at conflicting outcomes of genotoxicity assays and report diverging views and conclusions on the consequences of this genotoxicity issue for the ultimate safety assessment of chromium(III). The Panel notes that additional relevant *in vivo* studies have shown that exposure to chromium(III) chloride and chromium(III) nitrate induced DNA deletions in mice and yeast respectively and that it was recently reported that occupational exposure to chromium(III) can lead to DNA damage to human peripheral lymphocyte as evidenced by the Comet assay. The Panel is aware that given this situation the safety of chromium(III) might need to be re-evaluated in light of these recent reviews and evaluations.

DOCUMENTATION PROVIDED TO EFSA

Dossier on Chromium Nitrate. Proposed for Addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. June, 2005. Submitted by Health Food Manufacturers Association, UK.

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GLOSSARY / ABBREVIATIONS

AAS	Atomic Absorption Spectroscopy
ADI	Acceptable Daily Intake
AI	Adequate Intake
ANS Panel	Scientific Panel on Food Additives and Nutrient Sources added to Food
CAS	Chemical Abstracts Service
D-A-CH	Deutschland-Austria- Confoederatio Helvetica
EAR	Estimated Average Requirement
EC	European Commission
EFSA	European Food Safety Authority
EVM	UK Expert Group on Vitamins and Minerals
FNB	US Food and Nutrition Board
IARC	International Agency for Research on Cancer
ICP-AES	Inductively Coupled Plasma Atomic Emission Spectrometry
IOM	Institute of Medicine
IR	Infrared
JECFA	Joint FAO/WHO Expert Committee on Food Additives
SCF	Scientific Committee on Food
UL	Tolerable Upper Intake Level
WHO	World Health Organization