

**Opinion of the Scientific Panel on Food Additives,
Flavourings, Processing Aids and materials in Contact with Food
on a request from the Commission related to**

**Ferrous bisglycinate as a source of iron for use in the manufacturing of foods
and in food supplements**

Question number EFSA-Q-2005-039

Adopted on 6 January 2006 by written procedure

SUMMARY

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Foods (AFC Panel) has been asked to advise on the safety and bioavailability of ferrous bisglycinate when used as a source of iron in foods.

In 2004, The Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) evaluated the safety of iron in general, when present in fortified foods and food supplements, but considered that the available data were insufficient to establish a tolerable upper intake level for iron. The NDA Panel also indicated there are certain subgroups of the population (men and postmenopausal women) that may develop biochemical indicators of high iron stores by the additional intake of iron from food supplements. Based on estimates of current iron intakes in European countries, the NDA Panel concluded that the risk of adverse effects from high iron intake from food sources, including fortified foods in some countries, but excluding supplements, is considered to be low for the population as a whole, except for those homozygous for hereditary haemochromatosis.

The present opinion deals only with the safety and bioavailability of a particular source of iron, ferrous bisglycinate, intended for the general population, to be used in food supplements and in foods for particular nutritional uses. In addition, special attention has been paid to the use of ferrous bisglycinate as a source of iron in foods intended for infants and young children. The safety of iron itself, in terms of the amounts that may be consumed, is outside the remit of this Panel.

Ferrous bisglycinate consists of one molecule of ferrous iron bound to two molecules of glycine to form two heterocyclic rings. For food fortification and dietary supplementation, ferrous bisglycinate is formulated containing 77% ferrous bisglycinate and food-grade citric acid (17%), maltodextrin (2%), silicon dioxide (0.01%), and water (4%).

Studies to address the bioavailability and safety of ferrous bisglycinate have been conducted with ferrous bisglycinate. The absorption of iron from ferrous bisglycinate is regulated through the same physiological mechanisms as other inorganic forms of iron. Following oral administration, ferrous bisglycinate adds to the intestinal intraluminal pool of inorganic, non-haem iron and is absorbed intact into the mucosal cells of the intestine, and is subsequently hydrolysed into its iron and glycine components. The iron component of ferrous bisglycinate is metabolised like any other source of iron.

Use of an iron source such as ferrous bisglycinate should pose no safety concerns since the intended levels of use in foods are not anticipated to exceed those levels currently used for existing iron supplementation and food fortification programmes within the EU. Furthermore, following dissociation from ferrous bisglycinate, the free amino acid, glycine, will enter into normal metabolic processes.

Ferrous bisglycinate has been used in numerous field trials in developing countries for the iron fortification of foods providing between 2 and 23 mg/day of supplemental dietary iron without any reports of adverse effects. Additionally, dietary iron supplementation using ferrous bisglycinate, providing approximately 15 to 120 mg iron/day, has been well tolerated by adult males, pregnant females, non-pregnant females with normal iron statuses and more in particular by iron-deficient young children. In all cases substantial improvements in iron status indicators (serum levels of haemoglobin and ferritin, total iron binding capacity (TIBC), iron stores) were reported in the groups supplemented with ferrous bisglycinate compared to the controls. Moreover, there was no evidence of iron overloading in iron-replete individuals.

Ferrous bisglycinate has a low acute toxicity, with an oral LD₅₀ value of 2,800 mg/kg body weight in rats, corresponding to approximately 560 mg iron/kg body weight. The no-observed-adverse-effect-level (NOAEL) of 500 mg/kg body weight/day, which was reported for ferrous bisglycinate in a 90-day toxicity study in rats, corresponds to 100 mg iron/kg body weight/day, and provides a margin of safety that is 125-fold above the provisional maximum tolerable daily intake for iron of 0.8 mg/kg body weight established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

On the basis of the available studies on bioavailability, metabolism, toxicity, data on dietary supplementation and fortification studies in humans, including data from studies in foods intended for infants and young children, the AFC Panel considers that the use of ferrous bisglycinate, 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, meeting the specifications proposed, does not present a safety concern.

KEY WORDS

Ferrous glycinate, ferrous bisglycinate chelate, bis-glycino iron II, bisglycino-iron (II) chelate, CAS Number: 20150-34-9.

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 received a request for evaluation of ferrous bisglycinate as a source of iron in foodstuffs. The European legislative measures relevant to the uses indicated are:

- Commission Directive 2001/15/EC on substances that may be added for specific nutritional purposes in foods for particular nutritional uses (EC, 2001)¹,
- 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 (EC, 2002)²
- Commission Directive 91/321/EEC on infant formula and follow-on formula³

¹ OJ No L52, 22.2.2001, p19

² OJ L183, 12.7.2002, p51

- Commission Directive 96/5/EEC on processed cereal-based foods and other baby foods for infants and young children⁴

In addition, there is a Commission proposal for a regulation on the addition of vitamins and minerals and certain other substances to foods⁵.

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 ferrous bisglycinate when used as a source of iron in foods intended for the general population, food supplements, foods for particular nutritional uses including foods intended for infants and young children.

ASSESSMENT

The present opinion deals only with the safety and bioavailability of a particular source of iron, ferrous bisglycinate, intended for the general population, to be used in food supplements and in foods for particular nutritional uses. In addition, special attention has been paid to the use of ferrous bisglycinate as a source of iron in foods intended for infants and young children. The safety of iron itself, in terms of the amounts that may be consumed, is outside the remit of this Panel.

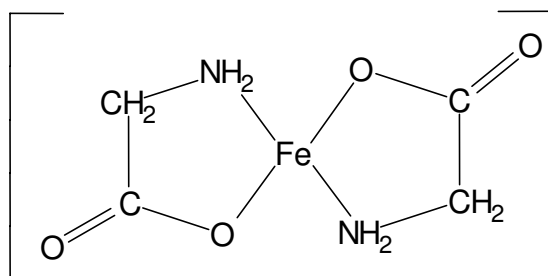
Chemistry

Chemical Name: Iron, bis(glycinato-N,O), CAS Number: 20150-34-9

Synonyms: ferrous glycinate, ferrous bisglycinate chelate, bis-glycino iron II, and bisglycino-iron (II) chelate.

Trade Name: ferrous bisglycinate

Molecular Formula: $\text{Fe}(\text{COOCH}_2\text{NH}_2)_2$



Structural formula

³ OJ L175, 4.7.1991, p 35

⁴ OJ L49, 27.7.1996, p 17

⁵ COM (2003)671 final

Ferrous bisglycinate consists of one molecule of ferrous iron bound to two molecules of glycine. The iron is bound to the carboxyl group and 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 neutralises the valence of ferrous iron and restricts its reaction with dietary inhibitors of iron absorption.

Specifications

According to the petitioner the commercial food-grade formulation of ferrous bisglycinate consists of 77% ferrous bisglycinate chelate, 17% citric acid, and a mixture of formulation aids consisting of silicon dioxide (0.01%) and maltodextrin (2%). The remaining portion is water (4%). The content of ferric ion is below 4%. All substances in the formulation are approved food additives in the European Union (EU), meeting food-grade specifications, with the exception of maltodextrin, which is a form of partially hydrolysed starch that is considered to be a food and therefore, specifically exempted from the food additive regulations.

Purity

The petitioner states that the purity of ferrous bisglycinate is greater than 80% on a dry weight basis taking into account the presence of citric acid (17%) added during the manufacturing process.

Impurities

According to the petitioner, on a dried basis, the only impurity found in significant amounts resulting from the manufacturing process is ferric iron the level of which is controlled within the specification. Specific tests have indicated that at least 97% of the iron is present in a chelated form.

Proposed Chemical and Microbiological Specifications and Analyses for Ferrous Bisglycinate

The petitioner provided analytical data of several non-consecutive batches of ferrous bisglycinate produced by the manufacturing process described below. The data show that the proposed specifications for ferrous bisglycinate are consistent with those recommended by the Joint FAO/WHO Expert Committee on Food Additives (FAO, 2003).

The petitioner provided analytical data of several non-consecutive batches of the commercial formulation of ferrous bisglycinate showing the absence in the final ferrous bisglycinate product of moulds and coliform bacteria as well as *Salmonella*, and *Staphylococcus aureus*.

Manufacturing Process

Raw materials used in the manufacturing process

According to the petitioner ferrous bisglycinate is manufactured, based on patented processes, from iron (II) and glycine, in the presence of citric acid to yield a ferrous bisglycinate preparation containing 23% ferrous iron and 60% glycine and 17% citric acid by weight.

Glycine (synthetic or natural) is already permitted in the EU for use in foods for particular nutritional uses as a source of amino acids under Directive 2001/15/EC (EC, 2001). Glycine and its salts (E640) are also permitted as food additives in the EU under Directive 95/2/EC (EC, 1995).

The petitioner states that the glycine used in the production of ferrous bisglycinate is in compliance with the EU specification as declared within Commission Directive 2000/63/EC, amending Directive 96/177/EC laying down specific purity criteria of food additives other than colours and sweeteners (EC, 2000). It is also stated that the glycine used to chelate the ferrous cation meets the United States Pharmacopoeia (USP) grade specifications and is equivalent to food-grade material.

According to the petitioner the high purity of reduced iron [$>96\%$ Fe(II)] also meets Food Chemicals Codex (FCC) specifications. Other processing chemicals (pH adjustment) meet specifications appropriate for food-use. All other ingredients used in the formulation of the commercial product, ferrous bisglycinate, meet specifications appropriate for food-use.

Manufacturing method

According to the petitioner, iron (II), in powder form, is reacted with a 2-fold molar excess of glycine in an aqueous environment where the pH is controlled through the addition of citric acid. Under these conditions, the iron forms a coordinate covalent complex with the ionised carboxylic acid moiety of glycine, and a coordinate covalent bond with the neutral amino group of glycine. The resulting product is dried to obtain a powder. Since ferrous bisglycinate is produced from reactions in an aqueous environment with subsequent drying to a powder, slight variations in product colour and particle size may be anticipated. The petitioner states that each manufactured lot is tested to indicate that it meets the current specifications for ferrous bisglycinate. Ferrous bisglycinate is manufactured under current good manufacturing practices.

Methods of analysis in food

According to the petitioner the level of total iron added to a foodstuff as ferrous bisglycinate may be determined using standard atomic absorption spectroscopy (method is described by petitioner). The method is directly applicable to a large number of metals in a number of different aqueous and solid food matrices. Using this method, the level of iron fortification can be compared directly to non-fortified foods.

Reaction and fate in foods to which the source is added

Stability, degradation or formation of reaction products

The stability of ferrous bisglycinate (by addition of the product to milk, yoghurt, corn flour, margarine) and the lack of potential for interaction of ferrous bisglycinate with these foods (lipid peroxidation) have been tested at various times/temperatures. There is no evidence to indicate the occurrence of reactions of ferrous bisglycinate with components of these foods (Ashmead and Ashmead, 1995; Hendricks and Ashmead, 1995; Name, 1996; Marchetti *et al.*, 2000; Latham *et al.*, 2001).

Ferrous bisglycinate has been reported not to affect the organoleptic properties of food products (maize meal) (Bovell-Benjamin *et al.*, 1998; Umbelino *et al.*, 2001). Additionally, the addition of ferrous bisglycinate to a fruit-flavoured drink powder and an animal feed supplement produced no effect on their vitamin and mineral contents (Latham *et al.*, 2001).

The solubility and stability of ferrous bisglycinate is pH-dependent. Ferrous bisglycinate is unstable at pH below 3 or above 10, due to breakage of chelate bonds. Studies in simulated gastric juice indicate that ferrous bisglycinate is stable in the stomach as a result of its buffering capacity and that of other food components. Although ferrous bisglycinate is heat-stable to temperatures above 220°C, the commercial formulation of ferrous bisglycinate contains other components that are labile at lower temperatures. It is

therefore recommended to keep processing temperatures for ferrous bisglycinate containing food products below 153°C. Most processed foods do not reach internal temperatures above 153°C. This has been verified for processes including pasteurisation, frying, and baking techniques (Name, 1996).

Case of Need and Proposed Uses

Justification for ferrous bisglycinate

The petitioner states that ferrous bisglycinate is intended for use in foods and beverages as a nutrient source, or as a food (dietary) supplement. It is further stated that ferrous bisglycinate provides a highly bio-available and stable source of iron (Bovell-Benjamin *et al.*, 2000; Layrisse *et al.*, 2000; García-Casal and Layrisse, 2001; Jeppsen, 2001). The 1:2 metal to ligand ratio present in ferrous bisglycinate lowers the potential of Fe(II) to participate in oxidation reactions and protects gastrointestinal surfaces from irritation by the iron (Jeppsen, 2001; Allen, 2002).

Intended uses and mode of incorporation

The petitioner states that ferrous bisglycinate is intended for use as a direct replacement for permitted iron forms (typically sulphate) in all categories of foods for particular nutritional uses (PARNUTS) (*Council Directive 89/398/EEC*), food supplements (*Council Directive 2002/46/EC*), and for food fortification purposes (once the Regulation has been adopted).

Information on Existing Authorisations and Evaluations

Ferrous bisglycinate has been granted registration by the People's Republic of China under the Law of Food Sanitation and has been incorporated into the Sanitation Guidelines for Using Food Additives (Motyka, 2001). In addition, the Brazilian State of São Paulo has mandated the use of ferrous bisglycinate-fortified milk in state-supported assistance programs for the prevention and treatment of iron deficiency and iron-deficiency anaemia in young children (Pineda, 2001). Other countries that currently utilise ferrous bisglycinate for the iron fortification of foods include those in Latin America (Argentina, Chile, Colombia, Ecuador, Mexico, Paraguay, Venezuela), European (Italy, Spain), and Asia (Thailand), as well as Saudi Arabia and South Africa (Motyka, 2001; Pineda, 2001; Allen, 2002).

In 1999, ferrous bisglycinate was considered to be Generally Recognized as Safe (GRAS) by the U.S. Food and Drug Administration (FDA) for use as a source of dietary iron for food enrichment and fortification purposes (GRAS No. GRN 000019).

In 2003, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated the use of “ferrous bisglycinate (processed with citric acid)” as a source of iron for supplementation and fortification purposes and had no safety concerns provided that the total intake of iron does not exceed the provisional maximum tolerable daily intake (PMTDI) of 0.8 mg/kg body weight (JECFA, 2004).

In 2004, the Scientific Panel on Dietetic Products, Nutrition and Allergies of EFSA concluded, however, that the available data are insufficient to establish a tolerable upper intake level of iron. Based on estimates of current iron intakes in European countries, the risk of adverse effects from high iron intake from food sources, including fortified foods in some countries, but excluding supplements, is considered to be low for the population as a whole, except for those homozygous for hereditary haemochromatosis (up to 0.5% of the population). However, intake of iron from food supplements in men and postmenopausal women may increase the proportion of the population likely to develop biochemical indicators of high iron stores. Some groups at special risk for poor iron status, such as menstruating women or children, could benefit from

additional iron intake and/or improved availability of dietary iron (EFSA, 2004). The Scientific Committee on Food recommended daily intakes of 6 mg and 4 mg for infants aged 0.5-1 year and 1-3 years respectively, assuming 15% absorption of the daily intake. For adults, assuming 10% absorption, the recommended dietary iron intake has been estimated as between 8 and 10 mg Fe/day (SCF, 1993)

Biological and toxicological data

Metabolic fate and biological distribution

As a non-haem source of iron, ferrous bisglycinate adds to the intestinal intraluminal pool of inorganic, non-haem iron. Using iron fortification doses ranging from 0.5 to 100 mg, providing iron at a ferrous bisglycinate/ferrous sulphate (FeSO_4) ratio of 1:200 to 1:10, it was demonstrated that ferrous bisglycinate competes with FeSO_4 for the non-haem iron absorption pathway (Pizarro *et al.*, 2002).

In studies in which $^{59}\text{FeSO}_4$ and ^{55}Fe -bisglycinate were administered together in a whole-maize or wheat-flour meal, iron absorption from ferrous bisglycinate was significantly higher than that from FeSO_4 (Bovell-Benjamin *et al.*, 2000; Layrisse *et al.*, 2000). There was no exchange of radiolabelled iron (*i.e.*, ^{59}Fe and ^{55}Fe) noted between ferrous bisglycinate and FeSO_4 in the non-haem iron pool prior to intestinal absorption, indicating that ferrous bisglycinate was absorbed intact into the mucosal cells of the intestine (Bovell-Benjamin *et al.*, 2000; Layrisse *et al.*, 2000). However, lower iron absorption values were obtained with ferrous bisglycinate (in enteric capsules) as the source at the intestinal level, compared to those obtained with FeSO_4 (in enteric capsules) (Pizarro *et al.*, 2002).

Following absorption into the mucosal cells, the iron is dissociated from ferrous bisglycinate and then distributed, reversibly bound to transferrin, for utilisation in proteins, including storage proteins (IOM, 2001; MacPhail, 2001).

Bioavailability of Iron from Ferrous Bisglycinate Following Oral Consumption

In two separate studies in groups of 9-month-old infants with normal iron status, Fox *et al.* (1998) compared the bioavailability of iron from commercial puréed vegetable meal (comprising parsnips, potatoes, cauliflower and milk) or whole-grain cereal (made from wheat, rye, oats, rice, wheat bran, and milk) fortified with respectively ferrous bisglycinate and FeSO_4 . In the first study the percentages of mean incorporation of iron into haemoglobin for FeSO_4 (9.1%) and ferrous bisglycinate (9.8%) were reported not to be significantly different when administered to the infants in a puréed vegetable weaning food. Lower iron bioavailabilities were reported for FeSO_4 (3.8%) and ferrous bisglycinate (5.2%) administered to infants in a whole-grain cereal meal. However, this difference in bioavailability was not statistically significant between the two iron compounds. The authors attributed the significantly lower iron bioavailability noted from the whole-grain cereal meal to its significantly higher phytic acid content (0.6%) compared to that of the puréed vegetable meal (0.15%).

Similarly, in comparative bioavailability studies in adult humans, the absorption of iron from ferrous bisglycinate has been reported to be significantly higher than that from FeSO_4 when administered together in a whole-maize or wheat-flour meal (Bovell-Benjamin *et al.*, 2000; Layrisse *et al.*, 2000). In a manner comparable to other iron compounds, the absorption of iron from ferrous bisglycinate is regulated physiologically by the body's iron status, with a negative correlation between iron absorption and serum ferritin (Olivares *et al.*, 1997; Iost *et al.*, 1998; Bovell-Benjamin *et al.*, 2000; Layrisse *et al.*, 2000; Giorgini *et al.*, 2001; Olivares and Pizarro, 2001).

Additionally, ferrous bisglycinate is highly soluble at physiological pH, which results in high iron bioavailability in foods despite the presence of such inhibitory factors as phytic acid. Also, the 1:2 metal to ligand ratio in ferrous bisglycinate restricts reaction with dietary inhibitors of iron absorption, resulting in

enhanced bioavailability (Bovell-Benjamin *et al.*, 2000; Layrisse *et al.*, 2000; García-Casal and Layrisse, 2001; Jeppsen, 2001).

Interactions with Other Components in the Diet

According to the petitioner, owing to its chemical structure, ferrous bisglycinate is protected from oxidation and other chemical reactions with compounds in the food matrix, and is stable. It was shown by Ashmead & Ashmead, (1995) and by Marchetti *et al.* (2000) that the addition of ferrous bisglycinate to multivitamin preparations does not affect the stability of vitamins. Additionally, fortification with ferrous bisglycinate had no effect on the availability of intrinsic zinc and calcium in yoghurt and milk (Drago and Valencia, 2002).

Impact on the intestine and on the absorption of other nutrients

The petitioner states that the absorption of ferrous bisglycinate is not expected to produce any significant effects on the absorption of other nutrients in the intestines.

Acute Toxicity

The oral LD₅₀ for ferrous bisglycinate was determined to be 2,800 mg/kg body weight in male and female rats, which corresponds to approximately 560 mg iron/kg body weight (with 95% confidence limits of 399 to 786 mg/kg body weight) (Kukulinski and Waller, 1993; Jeppsen and Borzelleca, 1999; EVM, 2003). Signs of toxicity observed in the rats included hunched posture, hypoactivity, hypothermia, prostration, poor coordination, and loose stools.

Subchronic Toxicity

In a 14-day range finding study, groups of CD Sprague-Dawley rats (3/sex/group) were given 0, 300, or 500 mg/kg body weight of ferrous bisglycinate orally by gavage (approximately 0, 60, and 100 mg iron/kg body weight/day, respectively). No deaths occurred during the study, and with the exception of a red focus in the glandular portion of the stomach and thick black material in the caecum of 1 high-dose female rat (500 mg/kg body weight), no other clinical findings were reported in any of the treated rats.

Based on the results of the 14-day range-finding study, groups of CD Sprague-Dawley rats (20/sex/group) were given ferrous bisglycinate in the diet at concentrations of 0, 100, 250, or 500 mg/kg body weight/day for a period of 13 weeks. The actual daily intake of ferrous bisglycinate was reported to be 0, 99.6, 249, and 497 mg/kg body weight in male rats, and 0, 99.4, 247.3, and 499.4 mg/kg body weight in female rats. This study was conducted in compliance with the U.S. FDA Regulations for Good Laboratory Practices (GLP) (21 CFR Part 58).

The animals were provided with water *ad libitum*. The rats were observed for signs of pharmacological or toxicological effects, morbidity and mortality twice daily and a thorough physical examination was performed prior to initiation of the study, as well as weekly thereafter. Food consumption was measured twice and body weights were measured prior to the start of the study, and weekly thereafter. Ophthalmoscopic examinations were performed on each animal prior to and at the end of 13 weeks of treatment. Haematological and clinical chemical parameters were determined.

Significant increases in food consumption were observed in male rats at all dose levels and in high-dose female rats at several intervals throughout the study, which were not considered to be toxicologically significant. Mean hepatic non-haem iron concentrations were increased approximately 1.6-fold in mid- and high-dose male rats, and about 1.4-fold in high-dose female rats treated with ferrous bisglycinate, compared with controls. However, according to the authors, these increases were not linearly related to dose, indicating the existence of a physiological control on the absorption and distribution of the iron from ferrous bisglycinate. No significant differences in mean haemoglobin concentration and haematocrit were reported between control and ferrous bisglycinate-treated rats. Slight but statistically significant increases in mean corpuscular volume and haemoglobin were reported in high-dose male rats compared to controls, but these values remained within normal range values, and were therefore not considered toxicologically

significant. Compared to controls, low- and mid-dose male rats exhibited significantly decreased levels of potassium, and mid-dose male rats also had significantly decreased aspartate-aminotransferase levels; however, these effects were not related to dose, and were considered not to be toxicologically significant. Two mid-dose female rats had significantly increased absolute and relative spleen weights compared to controls, but these effects were not considered to be toxicologically significant due to the absence of a dose-response relationship. Histopathological examination revealed no biologically or statistically significant, dose-dependent, macroscopic or microscopic findings that could be attributed to treatment with ferrous bisglycinate. The authors reported a NOAEL of 500 mg/kg body weight/day for ferrous bisglycinate in rats, corresponding to approximately 100 mg iron/kg body weight/day (Jeppsen and Borzelleca, 1999; Mandella, 2000).

Chronic Toxicity and Carcinogenicity

There are no chronic toxicity or carcinogenicity studies available on ferrous bisglycinate.

Reproduction and Developmental Toxicity

No reproductive or developmental toxicity studies are available on ferrous bisglycinate.

Other Studies

Human Studies

Ferrous bisglycinate has been used in numerous field trials as a source of iron for food enrichment and fortification purposes in various countries, including Guatemala (Pineda *et al.*, 1994; Pineda and Ashmead, 2001), New Zealand (Heath *et al.*, 2001), Brazil (Fisberg *et al.*, 1995; Queiroz and Torres, 1995; Gualandro and Name, 1996; Ashmead *et al.*, 1997; Iost *et al.*, 1998; Giorgini *et al.*, 2001; Szarfarc *et al.*, 2001; Miglioranza *et al.*, 2003), Saudi Arabia (Osman and Al-Othaimen, 2002), and the United Republic of Tanzania (Latham *et al.*, 2001). Such studies have shown that the use of ferrous bisglycinate as a dietary supplement (at levels providing approximately 15 to 120 mg iron/day) or iron fortificant (at levels providing between 2 and 23 mg iron/day) in foods is well tolerated by iron-deficient young children, adult males and pregnant females, and non-pregnant females with normal iron status. Treatment with ferrous bisglycinate (supplied as ferrous bisglycinate) produced substantial improvements in the serum levels of haemoglobin and ferritin, as well as total iron binding capacity (TIBC) and iron stores in individuals who were iron-deficient at the start of the fortification or supplementation trial, with no evidence of iron overloading in iron-replete individuals (Szarfarc *et al.*, 2001).

Studies with infants and children

In a study in Guatemala, forty infants (aged 6 to 36 months) with iron deficiency anaemia received a single daily dose of 250 µg folic acid and 5 mg iron/kg body weight in the form of a syrup containing 30 mg iron/mL as FeSO₄ or ferrous bisglycinate for a period of 28 days. Haemoglobin levels were significantly increased in both FeSO₄- and ferrous bisglycinate-supplemented groups at the end of the treatment period compared to baseline, but did not differ between groups. The change in haemoglobin was reported to be inversely proportional to basal levels, regardless of the iron compound administered. Mean plasma ferritin levels were increased from baseline values in both treatment groups, but the increase was only statistically significant in the ferrous bisglycinate-treated group (Pineda *et al.*, 1994; Pineda and Ashmead, 2001).

In Brazil several studies were performed with large groups of infants and young children analysing the effect of an intake of iron fortified foods on iron-deficiency anaemia, serum ferritin levels or haemoglobin levels.

- In a study by Fisberg *et al.* (1995) 81 children (aged 2 to 6 years, 10% were diagnosed as having iron deficiency anaemia) received commercially prepared cheese fortified with ferrous bisglycinate

at a level providing 2 mg of iron/90 g of cheese (approximately equivalent to 22.2 mg iron/kg of cheese) for 90 days. The daily iron intake from the cheese was about 2mg/person. At the end of 90 days, 6.3% of the children still presented iron deficiency anaemia and 20.5% were below normal ferritin levels. The improvements in average values of haemoglobin and haematocrit were not significantly different from pre-treatment levels; however, the increase in average serum ferritin levels from 15.69 to 24.68 ng/mL was statistically significant. There were no changes in the overall consumption of food by the children, although ratios of weight:age and weight:height increased as the study progressed, which the authors attributed to the reduction of iron deficiency parameters in the children. The authors concluded that ferrous bisglycinate was effective in increasing haemoglobin levels and replenishing iron reserves in the children.

- In a 12-month study by Queiroz and Torres, (1995) whole milk fortified with 3 mg iron/L milk as ferrous bisglycinate was provided daily (intake 1L/day) to 269 pre-schoolers (intake 1L/day). The prevalence of anaemia was significantly reduced in the children, from 62.3% at the beginning of the study to 26.4% at the end of the study.
- In a study with 434 youngsters (9% aged from 1 to 3 years and 16% aged >15 years) receiving iron-fortified sweetened peanut butter (45 mg iron/day as FeSO₄ or 23 mg iron/day as ferrous bisglycinate) for an unspecified duration, Gualandro and Name (1996) found that both compounds were well tolerated and that 23 mg of iron as ferrous bisglycinate was as effective as 45 mg of iron as FeSO₄ in correcting iron-deficiency anaemia.
- Iost *et al.*, (1998) provided daily for 7.3 months, ferrous bisglycinate-fortified milk (3 mg iron/L, milk intake 1L/day) to 185 infants and young children (aged 6 months to 2 years). At mean 222 days of the study, significantly increased haemoglobin concentrations were noted in children who were initially diagnosed with severe or less severe anaemia; however, no significant changes in mean haemoglobin concentration were reported in children with initially normal haemoglobin levels. From the study it was concluded by the authors that the fortification of commercial milk with ferrous bisglycinate was an effective dietary intervention for the treatment of iron deficiency and iron-deficiency anaemia in children.
- In a study by Giorgini *et al.*, (2001) 89 pre-school children (aged 1 to 6 years) were given (twice daily, 5 days a week, for 6 months), sweet rolls prepared from ferrous bisglycinate-fortified flour. At the end of 6 months, mean values of body weight:age and height:age ratios were significantly increased compared to pre-intervention values. Mean haemoglobin levels also were significantly increased and the prevalence of iron-deficiency anaemia was significantly decreased (from 28 to 9%). Similarly, the prevalence of low iron stores was significantly decreased (from 62 to 25%) in all subjects. The average increase in haemoglobin levels was reported to be significant for all 89 children studied, with the greater mean increase occurring in anaemic children. Significant increases also were reported for the mean serum ferritin levels of all subjects, particularly in children with depleted iron stores (mean increase of 13.03 µg/L). According to the authors, the greater increase in serum ferritin levels observed in children with lower basal levels of ferritin (as compared to ferritin increases in subjects with more normal levels) is consistent with the regulation of iron absorption from ferrous bisglycinate by iron stores
- Children and adolescents (467 subjects aged 7 to 14 years) participated in a 12-month fortification study conducted by Miglioranza *et al.*, (2003). The meals provided to the participants were reported to be this population's only access to food. The participants received 100 mL/day of a cheese whey drink containing 12 mg of iron as ferrous bisglycinate, 32 mg vitamin C, 400 µg vitamin A, and 5 µg vitamin D, as well as 8 g carbohydrates, 0.9 g protein, 0.5 g minerals, 0.2 g fat, and 15% frozen strawberry pulp. The prevalence of anaemia in the study population was assessed at the beginning of the study (baseline), and after 3, 6, and 12 months. No significant change in the prevalence of anaemia was reported after 3 months of fortification. However, significant decreases relative to baseline were noted after 6 (26.4%) and 12 months (9.6%) of fortification. Significant increases in haemoglobin levels were noted in all individuals after 3, 6, and 12 months of the study; however, after 12 months, the change was reported to be significantly higher in those whose baseline

haemoglobin levels were below 11 g/dL (increase of 2.2 g/dL) compared to those whose baseline haemoglobin levels were between 11 and 11.9 g/dL (increase of 1.32 g/dL), or those with levels above 12 g/dL (increase of 0.35 g/dL), which was indicative of the regulation of iron from ferrous bisglycinate by iron status. According to the authors, there was no significant decrease in the prevalence of anaemia in the study population after 3 months of fortification since the subjects received a low quantity of iron (12 mg/day) for a relatively short period of time. Additionally, it was suggested that the presence of calcium in the whey drink might have contributed to a decrease in iron absorption in the subjects after 3 months; however, calcium does not seem to influence overall iron status in individuals at longer periods of exposure to a continuous, low supply of iron.

In Tanzania a randomised double-blind placebo-controlled study was conducted for 6 months in 775 children (aged 6 to 12 years). Each child received daily 25 g of a placebo or fortified powdered orange drink, providing 0 or 5.4 mg iron/day as ferrous bisglycinate. The fortified powder also contained 1,750 IU vitamin A, 45 µg iodine, 5.25 mg zinc, 72 mg ascorbic acid, 0.6 mg riboflavin, 0.14 mg folic acid, 3 µg vitamin B₁₂, 0.7 mg vitamin B₆ and 10.5 mg vitamin E. Pre-treatment levels of serum retinol and measures of iron status, as well as anthropometric parameters were not significantly different between groups receiving the placebo and fortified orange drink treatment. The mean haemoglobin values of the fortified group significantly increased from 9.3 to 10.6 g/dL after the 6-month intervention period compared to those of the placebo group, whose mean haemoglobin levels only increased by 0.02 g/dL. There also was a significant increase in mean serum ferritin levels in the fortified group (by 16 µg/L) at the end of 6 months of intervention compared to that noted in the placebo group (by 2 µg/L). Additionally, the fortified group had significantly lower incidences of vitamin A deficiency at the end of the 6-month period compared to the placebo-treated group, as the number of children with serum retinol levels <20 µg/dL (indicating vitamin A deficiency) was decreased by 50% in the former group. Highly significant increases in weight gain, height gain, and Body Mass Index (BMI) also were noted in the micronutrient-fortified group compared with the placebo group at the end of the fortification trial (Latham *et al.*, 2001).

Milk fortified with ferrous bisglycinate (30 mg /L) was provided daily to 131 children, aged 6 to 14 years, in Riyadh, Saudi Arabia, for a period of 3 months. Milk was served and consumed 3 times daily. The total daily iron consumption was formulated to be 6 mg per child. Ferrous bisglycinate-fortified milk was reported to be well accepted by the children with no reports of any gastrointestinal problems during the course of the study. The authors reported no clinical indications of iron overload in any of the children in the study. The prevalence of those children with haemoglobin values <12 g/dL significantly dropped from 25.3 to 5.0% and 23.0 to 8.6%, for boys and girls, respectively ($p < 0.0001$). The authors concluded that fortification of milk with ferrous bisglycinate was an effective way to improve the haemoglobin levels of children with low or close to normal haemoglobin levels (Osman and Al-Othaimeen, 2002).

The above studies indicate that iron from ferrous bisglycinate is bioavailable and is able to reduce the prevalence of iron deficiency and iron deficient anaemia.

DISCUSSION

Following oral administration, ferrous bisglycinate adds to the intestinal intraluminal pool of inorganic, non-haem iron, is absorbed intact into the mucosal cells of the intestine, and is subsequently dissociated into its iron and glycine components. The iron component of ferrous bisglycinate is metabolised like any other source of iron, the safety and Maximum Tolerable Intake of which has been reviewed and evaluated by a number of scientific committees (JECFA, 1970, 1973, 1974, 1983; EVM, 2003; SCF, 1993; IOM, 2001; EFSA, 2004).

The absence of toxicity data on reproduction, developmental toxicity, chronic toxicity and carcinogenicity is not of concern, given the metabolism of ferrous bisglycinate into iron and glycine, which are both normal products of the body's metabolism, and given the homeostatic mechanisms that regulate tissue concentrations and body stores of iron (EFSA, 2004).

Ferrous bisglycinate has been used in numerous field trials in developing countries for the iron fortification of foods providing between 2 and 23 mg/day of supplemental dietary iron without any reports of adverse effects. Additionally, dietary iron supplementation using ferrous bisglycinate, which provides approximately 15 to 120 mg iron/day, has been well tolerated by iron-deficient young children, adult males and pregnant females, and non-pregnant females with normal iron status. In all cases, substantial improvements in iron status indicators, including serum levels of haemoglobin and ferritin, as well as TIBC and iron stores were reported in the groups supplemented with ferrous bisglycinate compared to the controls. Moreover, there was no evidence of iron overloading in iron-replete individuals.

In 2004, EFSA's NDA Panel evaluated iron in relation to the possibility for the derivation of a tolerable upper intake level. It considered that the available data were insufficient to establish a tolerable upper intake level for iron. It concluded that, based on estimates of current iron intakes in European countries, the risk of adverse effects from high iron intake from food sources, including fortified foods in some countries, but excluding supplements, is considered to be low for the population as a whole, except for those homozygous for hereditary haemochromatosis. However, intake of iron from food supplements in men and postmenopausal women may increase the proportion of the population likely to develop biochemical indicators of high iron stores. On the other hand, some groups at special risk for poor iron status, such as menstruating women or children, could benefit from additional iron intake and/or improved availability of dietary iron.

CONCLUSION

On the basis of the available studies on bioavailability, metabolism, toxicity, data on dietary supplementation and fortification studies in humans, including data from studies in foods intended for infants and young children, the AFC Panel considers that the use of ferrous bisglycinate, 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, meeting the specifications proposed, does not present a safety concern.

DOCUMENTATION PROVIDED TO EFSA

Letter from the European Commission to the Chairman of the European Food Safety Authority on the Commission request for a scientific opinion, based on its consideration of the safety and bioavailability of ferrous bisglycinate when used as a source of iron in foods intended for the general population, food supplements, foods for particular nutritional uses including foods intended for infants and young children. SANCO D4/HL/mm/D440061 (2005).

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