Iron Amino Acid Chelates

Eva Hertrampf and Manuel Olivares

Institute of Nutrition and Food Technology (INTA), University of Chile

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Abstract: Iron amino acid chelates, such as iron glycinate chelates, have been developed to be used as food fortificants and therapeutic agents in the prevention and treatment of iron deficiency anemia. Ferrous bis-glycine chelate (FeBC), ferric tris-glycine chelate, ferric glycinate, and ferrous bis-glycinate hydrochloride are available commercially. FeBC is the most studied and used form. Iron absorption from FeBC is affected by enhancers and inhibitors of iron absorption, but to a lesser extent than ferrous sulfate. Its absorption is regulated by iron stores. FeBC is better absorbed from milk, wheat, whole maize flour, and precooked corn flour than is ferrous sulfate. Supplementation trials have demonstrated that FeBC is efficacious in treating iron deficiency anemia. Consumption of FeBC-fortified liquid milk, dairy products, wheat rolls, and multi-nutrient beverages is associated with an improvement of iron status. The main limitations to the widespread use of FeBC in national fortification programs are the cost and the potential for promoting organoleptic changes in some food matrices. Additional research is required to establish the bioavailability of FeBC in different food matrices. Other amino acid chelates should also be evaluated. Finally there is an urgent need for more rigorous efficacy trials designed to define the relative merits of amino acid chelates when compared with bioavailable iron salts such as ferrous sulfate and ferrous fumarate and to determine appropriate fortification levels

Key words: iron amino acid chelate, iron absorption, food fortification, iron deficiency anemia.

Introduction

Iron amino acid chelates, such as iron glycinate chelates, have been developed as food fortificants and therapeutic agents for the prevention and treatment of iron deficiency anemia. At present the iron chelates that are available commercially are ferrous bis-glycine chelate (Ferrochel®) and ferric tris-glycine chelate (Fe amino acid chelate Taste Free®), both patented and produced exclusively by a private company (Albion Laboratories, Clearfield, UT) and ferrous bis-glycinate hydrochloride (Bioiron MS®, Kelatron Corp. South Ogden, UT). Ferric glycinate is another existing iron chelate (Patent N 249.049/96 University of Buenos Aires-SANCOR C.U.L., Argentina) that is produced and used industrially in fluid milk fortification by a dairy products company in Argentina. Its exact chemical nature has not been defined.

Ferrous bis-glycine chelate (FeBC) is a ferrous chelate formed by two glycine molecules bound to a ferrous cation, resulting in a double heterocyclic ring compound. The carboxyl group of glycine is linked with iron by an ionic bond, whereas the α-amino group is joined with the metal by a coordinate covalent bond [1]. The iron content is 20%. It is completely soluble in aqueous media at pH 2–6. Resistance to pH changes allows the chelate to maintain its capability of keeping iron in a soluble form and protecting it from dietary inhibitors. This property is believed to account for the high bioavailability of the iron in some food matrices.

In 1999, the FDA assigned generally regarded as safe (GRAS) status to FeBC, based on the self-affirmation process in which evidence of safety is provided by the applicant company. FeBC is being used currently to fortify several commercial products (Table I).

Ferric tris-glycine chelate (FeTC) is a ferric chelate of glycine with an iron content of 19%. It is 87% soluble at pH 2–5, but only 5% soluble at pH 7. It is not FDA-approved but is used as a food fortificant in some countries.

Ferrous bis-glycinate hydrochloride, a newly developed product, is completely soluble in water at pH 2–5. The iron content is 17–19%. The producer, (Bioiron MS®, Kelatron Corp. South Ogden, UT) is in the process of

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Table I: Products fortified with iron aminochelates

Type of food	Fortificant and level of Fe elem	Country	Observations
Milk			
Parmalat UHT	6 mg /L*	Brazil	
Parmalat UHT	6 mg /L*	Argentina and Chile	Zn 15 mg/L#
Parmalat UHT	3 mg /L*	Argentina, Colombia, Venezuela, México	
Parmalat UHT	7 mg /L*	Chile	
Parmalat UHT	10 mg /L*	Italy	
Nestlé, Batavo UHT	3.4 mg/L*	Brazil	
Goat Milk UHT	16 mg/L*	Brazil	Zn 15 mg/L#
Dos Pinos	12 mg/L*	Central America	
UHT	6 mg /L*	Saudi Arabia	
Spes Bona UHT	6 mg /L*	South Africa	
SANKOR UHT	Ferric Glycinate	Argentina	
Dairy Products			
Danone Petit Suisse Danonihno	2.7 mg /100g*	Brazil	
Nestlé Petit Suisse	2.8 mg /100g**	Brazil	
Nestlé Ninhio	2.8 mg/100g**	Brazil	
Nestlé Batavihno	2.7 mg/L*	Brazil	
Soprole Petit Forte	2.7 mg/100g*	Chile	
Yoplait Baby Up	1.7 mg/125 g**	Portugal	
Danone Yogurt Liquid	2.7 mg/100g*	Brazil	
Dutch Mill Yogurt Liquid	6.4 mg/160 g*	Thailand	
Other products			
Gessy Lever Margarina Clayb	2.0 mg /100g**	Brazil	
Finesse Granola bars	1 mg/bar*	Guatemala.	
Cookies Dona Benta	6 mg/ 100 g*	Brazil–UK	
Cookies Sam's Smart	4.18 mg /100 g*	South Africa	
Sugar, Turma de Monica	10 mg /kg.**	Brazil	
Procter and Gamble, powder drink	6 mg/ 25 g*	USA	
Corn flour	22 mg/kg	Costa Rica, México	

* Ferrous bis-glycinate chelate (Ferrochel®)
** Ferric trisglycinate (Iron aminoacid chelate Taste Free®),
# Zinc amino acid chelate Taste Free®

preparing a self-affirmed GRAS petition. *In vitro* tests have indicated that its bioavailability is similar to that of ferrous bis-glycinate, however, its bioavailability is also to be evaluated in human absorption studies. A new fortified juice powder containing ferrous bis-glycinate hydrochloride is ready for commercial release. Other commercial applications are under development (Brent Hagen, personal communication).

Iron absorption from amino acid chelates

Dietary iron absorption

There are two well-documented absorption pathways for iron (heme and non-heme). In the first pathway, heme is taken up intact into the enterocyte by an unknown mechanism. Once inside, it is moved to a microsomal compartment in the apical zone of the enterocyte where heme-oxygenase frees the iron from the tetraporphyrinic ring. It is incorporated into the pool of absorbed iron in the enterocyte [2]. Ferric non-heme iron is reduced at the intestinal brush border membrane by the duodenal cytochrome b (Dcytb), and then, together with luminal ferrous iron captured by divalent metal transporter 1 (DMT1) for cell uptake [3, 4]. The transporter competes with iron absorption inhibitors such as phytates, polyphenols, casein, etc., that are present in foods. This inhibitory effect can be counteracted by compounds that enhance the absorption of non-heme iron by keeping it in a soluble form and available for transport by DMT1. The principal iron-absorption enhancers are ascorbic acid, flesh derived from meat, fish or poultry, and organic acids including citric, malic, and lactic acids [5].

The intracellular common pool of absorbed iron derived from both heme and non-heme iron is either trans-

ported across the basolateral membrane of the enterocyte by ferroportin 1 (FPT1) to become bound to transferrin or incorporated into ferritin in the enterocyte. Enterocytic ferritin is excreted when the intestinal cells exfoliate into the bowel lumen. The absorption process appears to be regulated by hepcidin, which controls both enterocyte uptake by DMT1 and transfer to transferrin by FPT1.

Iron absorption pathways for amino acid chelates

The absorption pathway(s) for iron derived from the iron amino acid chelates have not been established clearly. FeBC has been studied in most of the absorption pathway experiments to date. It has been suggested that some or all of the iron in amino acid chelates is absorbed by a mechanism different from that for dietary heme and non-heme iron. Absorption could occur as the result of the uptake of the intact chelate by mechanisms that allow for the absorption of amino acids or oligopeptides. Bovell-Benjamin *et al* [6] hypothesized the existence of special non-heme iron receptors that take up iron from iron chelates at the intestinal mucosal surface. Bovell-Benjamin *et al* compared the absorption of 1 mg of radioisotopically labeled iron as $FeSO_4$ or FeBC that was added to a maize meal porridge. The compounds were administered to human subjects both in separate meals and combined in the same meal. Iron absorption from FeBC was four times higher than iron added as $FeSO_4$ when eaten alone and when eaten together with $FeSO_4$. These results were interpreted as evidence of the lack of exchange between iron chelates and the non-heme iron pool. The authors suggested that FeBC was absorbed intact by a different absorption pathway. We think that the experimental observations made by Bovell-Benjamin *et al* fail to provide convincing evidence for the existence of a separate absorption pathway for FeBC iron [8]. Only one low dose of iron (1 mg) was administered as either $FeSO_4$ or FeBC (1:1 ratio). Competition for an active transport pathway cannot be demonstrated under these conditions because the quantity of iron at this dose would not be sufficient to saturate the receptors and transporters of iron into the enterocyte. Recently, we studied the effect of graded doses of FeBC on the absorption of $FeSO_4$ (FeBC:$FeSO_4$ Fe ratios 10:1 to 200:1). The results demonstrate that iron given as FeBC competes with iron given as $FeSO_4$ for the non-heme iron absorption pathway in human volunteers [9].

There is increasing evidence supporting the notion that a significant fraction of the iron in the FeBC is dissociated in the gastrointestinal tract, where it can enter the common non-heme iron pool and interact with other dietary constituents [6, 7, 9–11]. Absorption from FeBC increased significantly when ascorbic acid was added to milk [10], and inhibited by milk, tea, coffee, and phytates [10–12]. When phytase was added to precooked corn flour fortified with FeBC, iron absorption increased by 61%. A similar percentage for absorption values was obtained for $FeSO_4$ [11]. Studies carried out in Chile may provide additional insight into the mechanism by which enhanced iron absorption is achieved with FeBC [10, 13, 14]. In these experiments, iron absorption from both FeBC and $FeSO_4$ was shown to be inhibited by milk while absorption from hemoglobin was not influenced (Table II). Since heme iron is absorbed intact, the iron is protected from the interaction with milk [14]. On the other hand percentage absorption values for both $FeSO_4$ and FeBC were reduced in the presence of milk components. However the inhibitory effect was less marked for FeBC than for $FeSO_4$. These results are consistent with the postulated alternative pathway for the absorption of some or all of the iron in FeBC. However there is another equally or perhaps more plausible explanation. Some of the chelated iron may have been released into the common pool in the stomach while the rest remained in the intact chelated form. The fraction entering the common pool would be affected by the diet. The continuously chelated iron fraction could be protected from interactions with dietary components, but nevertheless be released to DMT1 once the higher pH duodenal environment is reached. The absorption of the iron released into the common pool in the stomach would be affected in the same way as dietary iron. It would not be surprising if the extent of iron release from the chelate into the common pool varied in different food matrices, perhaps accounting for the inconsistencies in apparent bioavailability observed in the isotopic studies described below.

In summary the results of the studies discussed above do not permit the exclusion of the possibility that a fraction of the iron chelated within FeBC is absorbed through a pathway different from that of heme or non-heme iron. However the existence of FeBC-specific receptors or the presence of intact FeBC molecules within the enterocyte has not been reported. The better absorption of iron from FeBC may well be explained by its chemical structure, which protects a significant fraction of the iron from in-

Table II: Effect of milk on iron absorption

Iron compounds	Water (%)	Milk (%)	Ref
Ferrous sulfate	29.9	4.6	[13]
Ferrous Bis-glycine Chelate	34.6	8.3	[10]
Hemoglobin	22.3	21.0	[14]

teractions with dietary components, offering a greater amount of bioavailable iron for absorption by the enterocyte via the DMT1 pathway.

The results of absorption studies with FeTC have generally shown it to be a less bioavailable source of iron than FeBC. In our study, absorption of FeBC was as good as ferrous ascorbate in water, but that of FeTC was less than 50% of FeBC [10]. The poor absorption of FeTC in this experiment may be partially explained by its low solubility when the pH is greater than 2. Bovell-Benjamin *et al* [6] reported a higher absorption of iron from $FeSO_4$ (29.9%) than from either FeBC (10.1%) or FeTC (15.4%). We speculate that the surprisingly low iron absorption from FeBC in this experiment was due to inadequate stability of the chelate because it was held in water for a long time. FeTC was less well absorbed from whole maize meal porridge than FeBC (2.3% vs. 15.3%) [6]. Lower bioavailability of FeTC compared to FeBC was also observed in a petit suisse, a cow's milk cheese (Pizarro, F.; personal communication). Tea inhibits iron absorption from FeTC (Olivares, M.; unpublished results). All these observations indicate that FeTC is not a fortificant of choice because of its low bioavailability.

Regulation of iron absorption from amino acid chelates

Iron absorption of FeBC, FeTC, and ferric glycinate, when ingested mixed with water and foods, has been examined in studies in humans using iron isotopes [6, 10, 15]. There was an inverse relationship between the iron stores of the body, as reflected by serum ferritin and the absorption of the iron amino acid chelates in all of them. This also holds true for the comparison of the absorption of the chelated iron with that of ferrous ascorbate [10, 15]. All of these studies strongly suggest that iron absorption from amino acid chelates is controlled by iron stores.

Potential toxicity of iron glycine chelates

The acute toxicity of FeBC is related to its iron content. In rats, the oral LD50 was 560 mg iron, as FeBC, per kg body weight. Jeppsen and Borzelleca [16] evaluated the subchronic toxicity (90 days) of FeBC using a rat model. The results of this study suggest that an intake of FeBC up to 500 mg/kg body weight/day may be considered safe and that absorption of iron from FeBC is homeostatically regulated. This conclusion is supported by the human studies described earlier that strongly suggest that iron absorption from FeBC is regulated by iron stores, implying that the risk for iron overload resulting from the prolonged ingestion of FeBC is no different than that from other bioavailable iron compounds such as $FeSO_4$. The glycine moiety is a naturally occurring amino acid that is metabolized. Possible effects of FeBC on the absorption of essential trace elements such as zinc, copper, and magnesium, as well as some toxic metals such as lead and cadmium, have not been reported. Further research is needed.

Technical functionality of amino acid chelates

Stability during processing and storage

Data available in the literature on the technical functionality of iron glycinate chelates are very scarce. Only two studies evaluating whole maize flour and a model infant formula were found [21, 22]. Data on FeBC fortified milk and milk products are not available. However several fortified commercial products seem to have adequate consumer acceptability.

The effects of iron amino acid chelates on sensory properties and storage stability of maize corn and other high phytate foods were reported by Bovell-Benjamin *et al* [17]. A descriptive analysis of organoleptic qualities and hexanal production in whole maize porridge that was unfortified or fortified with 30 or 60 mg iron/kg as FeBC, FeTC, FeNaEDTA, and $FeSO_4$ was given. Samples were stored at 30, 40, or 50 °C for 20 days. The results showed that FeBC produced the most rancidity. They concluded that iron fortification with FeBC lowered the sensory quality and storage stability of maize. It is necessary to point out that the fat content of the most commonly consumed forms of maize in Central America and Mexico, degermed, pre-cooked corn flour and nixtamalized corn flour, is less than that of flour tested by Bovell-Benjamin *et al* [18]. Organoleptic changes were not observed in nixtamalized corn flour fortified up to 22 mg Fe as FeBC/kg [19]. Fortification of wheat flour fortified with up to 30 mg Fe as FeBC/kg did not affect color, peroxide formation, or dough viscosity [19]. Changes in specific volume of bread were not observed at Fe fortification levels below 22 mg/kg.

A study of the pro-oxidant properties of ferric glycinate, in a powdered casein-based infant formula (60 ppm), compared with those of ferrous sulfate was carried out in Argentina [20]. Fortified formulas were stored at 20, 37, and 45 °C for 12, 9, or 7 months, respectively. The samples were assayed periodically during storage for vitamins A, E, B_1, B_2, and C. The pro-oxidant effects of iron added as ferric glycinate were less than those of $FeSO_4$.

Further research is needed to establish the compatibility of iron amino acid chelates with different food matrices, particularly the corn flour products commonly used in South and Central America.

Iron absorption from amino acid chelates in human volunteers

Isotopic studies

Iron bioavailability studies using radio-iron techniques (Table III) have demonstrated that the absorption of iron from FeBC is superior to that of ferrous sulfate in some foods such as whole maize flour, precooked maize flour, wheat flour, and milk, that are known to contain iron absorption inhibitors [6, 10, 11]. Iron absorption from whole maize meal porridge and decorticated, de-germed, precooked corn flour (''arepas'') fortified with FeBC was higher when compared to $FeSO_4$ [6, 11]. Absorption from ''nixtamalized'' corn masa flour fortified with FeBC was low (1.3%), comparable to ferrous fumarate in the same vehicle [21]. Iron absorption from FeBC was less than that from FeNaEDTA in the precooked corn flour and in corn-masa flour [11, 21]. The fraction of iron absorbed from FeBC was twice that absorbed from ferrous sulfate in bread prepared with wheat flour and ingested with cheese. Absorption from FeNaEDTA was even higher [11]. Both FeBC and ferric glycinate [15] were well absorbed from milk. Percentage absorption was similar to that reported for milk fortified with $FeSO_4$ and ascorbic acid [22]. Iron absorption from $FeSO_4$ alone in milk was almost three times lower (4%). It is possible to compare the results of the two different studies because they were corrected to a 40% ferrous ascorbate reference dose absorption.

There was no significant difference in the bioavailability between ferrous sulfate and FeBC when added to either a low-phytate vegetable weaning food or a high-phytate whole-grain cereal weaning food in a study that employed stable isotopes [12].

In summary, the results of these isotopic studies indicate that FeBC is a source of bioavailable iron. The inter-study differences in the results are most consistent with the postulate that a variable fraction of the iron in the chelate is released into the common pool, exposing it to the inhibitors in the meal. The extent of the loss of chelated iron may depend on the food matrix.

Field studies

1) Supplementation. The use of FeBC as a supplement to treat anemia was reported in three studies in young malnourished children, pregnant women, and adolescents (Table IV). FeBC was well tolerated and there was an improvement in iron status in all of them [23–25]. However, these results must be interpreted with caution because of methodological restraints such as inadequate or absent control groups, high or unreported dropout rates, and the use of non-equivalent doses of iron when comparisons were made with $FeSO_4$. They do suggest that FeBC is efficacious in treating iron deficiency anemia, but do not permit one to conclude that FeBC is as efficacious as $FeSO_4$ even when smaller doses of the chelate are used.

2) Fortification: FeBC-fortified foods were evaluated in seven studies in children (Table V). An increase in hemoglobin levels and/or a reduction in the prevalence of anemia or iron deficiency was reported in all of them. The fortified foods were liquid milk, dairy products, and wheat flour sweet rolls [26–30]. The main limitation to the interpretation of these studies is the lack of control groups receiving the same food fortified with another compound of proven efficacy or a placebo. It is not possible to be certain that the improvements in hemoglobin levels and iron status were due only to food fortification with FeBC.

In two studies, a multinutrient-fortified beverage was given to 6- to 11-year-old children [31, 32]. An improvement in iron status despite an increase in the prevalence

Table III: Iron absorption from foods fortified with ferrous bis-glycinate and its absorption ratio to ferrous sulfate

	Fe Absorption (%)			
Food	Ferrous sulfate	Ferrous Bis-glycinate	Absorption Ratio	Reference
Pureed vegetables	9.9	9.0	0.9	Fox *et al* [12]
Whole grain infant cereal	3.8	5.2	1.4	Fox *et al* [12]
Whole-maize porridge	1.7	6.0	3.5	Bovell-Benjamin *et al* [6]
Pre-cooked corn flour + cheese	4.7	8.4	1.8	Layrisse *et al* [11]
White wheat flour + cheese	5.3	10.8	2.0	Layrisse *et al* [11]
Milk	3.6*	11.1	3.1	Olivares *et al* [10]
Corn masa flour		1.3		Walter *et al* [21]

* Value taken from reference 14

Table IV: Effect of supplementation trials with FeBC to prevent iron deficiency anemia

Author & study site	Sample	Study design and treatment	Design concerns	Outcomes measured	Results
Pineda *et al* Guatemala [23]	100 Guatemalan anemic adolescents divided into 4 groups	Comparison of different doses of iron from FeBC (120, 60, and 30 mg of Fe) and iron as ferrous sulfate (120 mg Fe). Follow-up for 4 weeks.	No info about drop-outs. Lack control group for 30 and 60 mg doses of FeBC.	Tolerance Hemoglobin and ferritin response	Hemoglobin response was similar in the 4 groups. Increases in ferritin values were similar except group receiving Fe 30 mg.
Pineda & Ashmead Guatemala [24]	2 groups of 20 anemic, malnourished Guatemalan infants, aged 6–36 months old.	Double-blind, comparison of syrups fortified either with ferrous sulfate or FeBC at 5 mg/kg body weight/day. Follow-up for 28 days.	No info about drop-outs. Etiology of anemia not clarified; anemia in malnutrition is multifactorial; mean ferritin values too high for IDA infants.	Hemoglobin and ferritin response	Both groups had significant increases in Hb levels. Only group treated with FeBC increased plasma ferritin level.
Szarfac *et al* Brazil [25]	145 healthy pregnant Brazilian women	Randomly assigned to 40 mg or 15 mg of Fe as ferrous sulfate and FeBC, for 13 weeks starting at 20th week	Too high drop-out rate > 50 %. Only 30% accepted venous puncture. Difference in doses of Fe and high drop-out rate makes interpretation difficult.	Tolerance Hemoglobin, SAT and ferritin response	Best tolerance in FeBC group. No difference in Hb. SAT and ferritin higher in FeBC group.

IDA= iron deficiency anemia
Hb = hemoglobin

of anemia after fortification was reported in one of the studies. Both studies included a control group. The increases in the prevalence of anemia, although less than that observed in the respective placebo groups, weaken the conclusions about the efficacy of the fortified beverage in the prevention of iron deficiency anemia.

In summary the seven fortification studies are not rigorous enough to permit definitive conclusions about the efficacy of FeBC fortification to be made. They do not allow conclusions to be drawn about the relative efficacy of FeBC with respect to $FeSO_4$ and they do not provide an adequate basis for making recommendations for levels of fortification with FeBC.

Cost

High cost is one of the main limitations to the widespread use of FeBC. It is approximately 20 times more expensive than $FeSO_4$ per unit of iron. Products from other companies are not readily available at present. Furthermore the use of FeBC in food fortification usually requires the addition of antioxidants or the application of special technologies in the process of fortification, which further increase the costs.

Recommendations for the use of iron amino acid chelates and for additional research

FeBC is a form of iron that is highly bioavailable. The preponderance of evidence suggests that the iron is absorbed by the DMT1 pathway and that it is regulated by body iron stores. The intact chelate probably does not enter the non-heme common pool. However a variable proportion of the iron in the chelate appears to be released into the common pool. The proportion of iron that is released may depend on the food matrix that is fortified.

FeBC is suitable for fortifying several commercial foods including liquid milk, dairy products, and flavored beverages that are reconstituted from dry powder. These vehicles allow the delivery of significant amounts of bioavailable iron. FeTC has not been studied rigorously, but the available evidence suggests that it is unlikely to be a source of highly bioavailable iron.

The small amount of information on ferric glycinate does not allow definitive conclusions to be drawn about the potential value of this chelate.

Table V: Efficacy studies of ferrous bis-glycine chelate (FeBC) fortified foods and powder beverages

Author & study site	Sample	Study design and treatment	Design concerns	Outcomes measured	Results
Liquid milk					
Iost C *et al* Brazil [26]	185 small children aged 9 mo to 4 years with normal to severe anemia	Liquid milk fortified with 3 mg/L Fe as FeBC during 222 days	No control group Drop-out not recorded	Hb response	Hemoglobin increased significantly at days 133 and 222
Osman AK, al-Othaimeen A [27] Saudi Arabia	131 children aged 6–14 years	Liquid milk fortified with 6 mg/L Fe as FeBC (1 L/day) during 3 months	No control group Drop-out not recorded	Acceptability and tolerance Hb and ferritin response	Anemia dropped in boys and girls (25 to 5%; 23–10%) Low ferritin values From 9 and 21 to 6 and 12%
Dairy products					
Fisberg M. *et al* [28] Brazil	81 children aged 2–6 years	Cheese type petit suisse fortified with 2 mg Fe as FeBC /90 g during 3 months	No control group Drop-out not recorded	Hb and ferritin response	Anemia decreased from 10 to 6%. Low ferritin values dropped (60 to 20%)
Miglioranza L.H. *et al* [29] Brazil	477 children aged 7–14 years	Frozen strawberry whey drink fortified with 12 mg Fe as FeBC/100 mL per day, during one year.	No control group Drop-out not recorded	Hb response	Anemia decreased from 42 to 10% after one year
Wheat flour sweet rolls					
Giorgini E. *et al* [30] Brazil	89 preschool children	Sweet rolls fortified with 2 mg Fe as FeBC per roll. Two rolls per day for 6 months.	No control group	Hb response	Anemia dropped from 28 to 9%
Micronutrient fortified beverages					
Ash DM *et al* [31] Tanzania	830 children aged 6 to 11 years	Randomized, double blind placebo controlled study. Beverage fortified with 5.4 mg of Fe as FeBC /25 g per day for 6 months. Consumption controlled.	Malaria and seasona effects confound the interpretation of hemoglobin	Hb, erythrocyte protoporphyrin, serum ferritin	Hb dropped and anemia increased in both groups after follow up, the deterioration was smaller in the fortified group. Iron nutrition indices improved significantly.
Abrams S. *et al* [32] Botswana	311 children aged 6–11 years	Exp group: one school received 240 mL beverage fortified with 7 mg Fe as FeBC daily for 8 weeks. Con group: other school received an isocaloric placebo.	Logistic problems difficult interpretation of hemoglobin values	Hb, serum ferritin, transferrin receptors	Anemia increased in both groups but it was significantly less in the Exp group Iron nutrition improved in the Exp group

Hb = hemoglobin

Ferrous bis-glycinate hydrochloride may prove to be a valuable source of bioavailable iron. The results of its initial evaluation in human subjects are eagerly awaited.

Additional research, including well-designed efficacy studies, are needed to establish the cost effectiveness of using FeBC in foods that can be fortified with bioavailable iron salts and to determine appropriate fortification levels.

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Eva Hertrampf

Instituto de Nutrición y Tecnología de los Alimentos (INTA)
Universidad de Chile
Macul 5540
Santiago, Chile
Fax 56-2-2214030
E-mail: ehertram@inta.cl