The Potential Role of NaFeEDTA as an Iron Fortificant

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Abstract: Ethylene diamine tetraacetic acid (EDTA) is a hexadentate chelator, which can combine with virtually every metal in the periodic table. $CaNa_2EDTA$ and Na_2EDTA (ADI 2.5 mg EDTA/kg body weight/day) are widely used as sequestering agents in canned products, while NaFeEDTA is a promising iron fortificant. Binding of EDTA with iron is favored in the acid milieu of the stomach, irrespective of whether the EDTA is administered as $CaNa_2EDTA$, Na_2EDTA, or NaFeEDTA, but in the more alkaline medium of the duodenum the iron is exchanged, in part, with other metals. The iron released from EDTA is absorbed by the normal physiological mechanisms. When NaFeEDTA is present in a meal, the iron moiety exchanges with the intrinsic food iron and the EDTA partially protects the iron in this common non-heme iron pool from the effects of inhibitors of iron absorption, such as phytates and polyphenols.

When iron is added as NaFeEDTA to an inhibitory meal, it is two to three times better absorbed than is iron added as ferrous sulfate. It also has a similar effect on the intrinsic food iron in the meal. Fortification with NaFeEDTA is most efficacious when administered with cereal- and legume-based diets but offers no advantages over other fortificants when added to meals of high bioavailability. Its potential as a fortificant has been confirmed in five extended fortification trials carried out in developing countries.

There is no evidence that NaFeEDTA in the dose range proposed for food fortificants (5 to 10 mg iron daily) will have any direct toxic effects. Na_2EDTA and $CaNa_2EDTA$ have proved safe over a number of years, while the Joint FAO/WHO Expert Committee on Food Additives concluded in 1999 that NaFeEDTA "could be considered safe when used in supervised fortification programs". Animal and human studies, including the results of two fortification trials, suggest that NaFeEDTA has little or no effect on overall zinc metabolism. Indeed, if anything, it increases zinc and possibly copper absorption. Data on potentially toxic metals, such as lead mercury, aluminum, and manganese, are limited but the evidence that is available is uniformly negative thus far. Further studies in this field are desirable. The long-term potential of NaFeEDTA fortification to cause iron overload is conjectural but the available evidence suggests that homeostatic controls would prevent excess iron accumulation in the normal population.

NaFeEDTA, which is pale yellow in color, causes fewer organoleptic changes in a number of stored vehicles, including cereals, than do other soluble iron salts. Other potential vehicles include condiments, several of which have been successfully used in fortification trials. What is currently lacking is a consolidated body of published evidence on the stability of NaFeEDTA during processing, storage, and household cooking in widely consumed food vehicles, coupled with standardized testing of consumer acceptance of each fortified vehicle.

While NaFeEDTA seems to be an appropriate fortificant for developing countries, its cost is about six to eight times that of ferrous sulfate in terms of equivalent amounts of iron. Its better absorption (a factor of 2–3) might make it possible to halve the daily fortification level but, it still remains expensive and there is a pressing need for food grade NaFeEDTA at more affordable prices.

Another possible option is the use of other salts of EDTA (Na_2EDTA or Ca Na_2EDTA) together with a soluble source of iron, such as ferrous sulfate. The combination has been shown to be as effective as NaFeEDTA

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when the EDTA:Fe molar ratio is between 1:2 and 1:1. This approach is, however, only feasible with vehicles that are stored for short periods because of ferrous sulfate's propensity to cause organoleptic changes. The search for an iron source that is more stable but at the same time available to combine with EDTA has been unsuccessful thus far.

Target populations for fortification with NaFeEDTA include all those that subsist on cereal- and legume-based diets, with the most appropriate vehicles being cereal products and condiments. The fortification of infant milk and cereal formulas with NaFeEDTA does not seem appropriate, since the amounts of NaFeEDTA required for effective fortification would be close to the acceptable daily intake (ADI) of 2.5 mg EDTA/kg body weight/day.

Key words: Iron deficiency, iron fortification, iron EDTA, NaFeEDTA, iron bioavailability.

Introduction

Iron fortification has been used for decades in a number of industrialized countries to combat iron deficiency and seems to have played a significant role in reducing its prevalence, especially in infants and women [1]. The overall strategy has been one in which staples, such as wheat flour, have been fortified with iron. While the overall effects appear to have been positive, evidence of benefit in developing countries is less convincing. Although there are probably several contributory factors, an important one is the lower bioavailability of typical diets consumed in such countries. In this context, the selection of the fortificant always represents a compromise between the choice of chemically reactive compounds of high bioavailability, such as ferrous sulfate, or inert compounds, which are poorly absorbed. Ferrous sulfate is very effective when added during the preparation of bread and bakery products and infant formulas, but cannot be used in stored flour because of organoleptic problems. As a result, inert, less well-absorbed compounds, such as elemental iron powders, must be used. The search, therefore, continues for compounds of high bioavailability that do not cause organoleptic changes in the vehicles to which they are added. In this regard, particular attention has been paid to the potential role of the iron chelate, NaFeEDTA, as a fortificant, especially in developing countries. It has several attractive properties. It can be added to several food vehicles without catalyzing the formation of undesirable flavors, colors, and odors, it is less affected by the inhibitors of iron absorption present in diets of low bioavailability, and it may actually enhance the bioavailability of intrinsic food iron in some low bioavailability foods. The potential role of NaFeEDTA as an iron fortificant was extensively reviewed in a monograph prepared by the International Nutritional Anemia Consultative Group in 1993 [2]. The Group concluded that there was "sufficient information to recommend the use of NaFeEDTA, also called iron EDTA, for food fortification in programs to improve iron status". In the discussion, which follows, this information will be analyzed together with further evidence that has been obtained in the last ten years.

Chemical Interactions of Iron and EDTA

Ethylene diamine tetraacetic acid (EDTA) was first synthesized and patented in Germany in the mid-1930s. At the time, it was recommended for use as a water softener and as a dyeing aid because of its ability to form stable and water-soluble complexes with metal cations [3]. Later, in 1974, two of its salts ($CaNa_2EDTA$ and Na_2EDTA) were evaluated as food additives by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and allocated an acceptable daily intake (ADI) of 2.5 mg EDTA/kg body weight/day. They have been widely used as sequestering agents to prevent organoleptic changes in canned products [4]. In addition, NaFeEDTA, an iron-EDTA chelate, is a promising iron fortificant, which has recently been reviewed by JECFA for government-approved fortification strategies [5].

EDTA is a hexacoordinating complexing agent. It can combine with virtually every metal in the periodic table, with the metal ions being bound via four carboxylate and two tertiary amine groups. The effectiveness of EDTA as a chelator for a particular metal depends on its stability constant with the metal. This is affected by pH, the molar ratio of the chelator to the metal ion, and the presence of competing metal ions and other ligands capable of forming complexes with EDTA [2, 6]. Of the nutritionally important metals, ferric iron has the highest stability constant of 25.1, followed by copper (18.4), zinc (16.1), ferrous iron (14.6), calcium (10.6), magnesium (8.7), and sodium (1.7) [7]. Potentially toxic metals, such as mercury (20.4), lead (18.0), aluminum (16.1), and manganese (13.5) also have high stability constants [3].

When EDTA chelates with ferric iron through six coordinate covalent bonds, it forms an octahedral complex, with the Fe^{3+} ion located in the center. While the iron-EDTA complex has the highest stability constant of all the metals, the situation is complicated by the fact that each metal has an optimum pH for chelate formation, ranging from pH 1 for ferric iron to pH 3 for copper, pH 4 for zinc, pH5 for ferrous iron, pH 7.5 for calcium, and pH 10 for magnesium [7]. Binding to iron is, therefore, favored in the acid environment of the stomach, but in the more alkaline surroundings of the duodenum the iron is exchanged in part for other metals.

Based on the pH optima for the binding of different metals, certain predictions can be made as to what happens in the intestine when NaFeEDTA or $CaNa_2EDTA$ are added to food [2]. In the stomach, ferric iron from NaFeEDTA remains firmly bound to EDTA, whereas the calcium and sodium from $CaNa_2EDTA$ dissociate and EDTA binds iron from the common pool of non-heme iron. Thus, even with the addition of $CaNa_2EDTA$, iron EDTA is formed in the stomach. In the duodenum, however, the iron is released and absorbed [8] and the EDTA is then presumably available to bind in succession to copper (pH 3), zinc (pH 4), ferrous iron (pH 5), and to calcium further down the gastrointestinal tract. Most of these metals are subsequently released for absorption, with less than 5% of metal/EDTA complexes being absorbed (< 1% NaFeEDTA), and the remaining 95% of the EDTA being excreted in the stool [8, 9]. Absorbed metal/EDTA complexes are rapidly excreted in the urine over 12 to 24 hours.

Effects on Iron Absorption

NaFeEDTA and the common iron pool

There is a solid body of evidence supporting the premise that soluble iron added to a meal and the intrinsic non-heme food iron form a common pool [10, 11] with both sources of iron being equally susceptible to the effects of enhancers (e.g., ascorbic acid and meat) and inhibitors (e.g., phytates and polyphenols) of iron absorption present in the meal. Iron administered as NaFeEDTA behaves in a similar fashion. When $Na^{59}FeEDTA$ has been added to meals intrinsically labeled with ^{55}Fe, the proportion of iron absorbed from the two sources has been close to unity [9, 12, 13]. While these results illustrate the reciprocal exchange that occurs between food iron and iron added as FeNaEDTA, the chelate has been shown to have a further important advantage. It can enhance the absorption of the intrinsic non-heme iron in food. In one experiment, ferrous sulfate, which joins the common pool of food iron, and NaFeEDTA were fed on separate days in the same type of meal (maize porridge) [9, 13]. Iron absorption from the NaFeEDTA-fortified meal was found to be significantly better. However, the iron from ferrous sulfate was as well absorbed as from NaFeEDTA when they were fed together in the same meal [9, 13]. These results indicate that EDTA equilibrates with iron in the common pool and thereby increases the bioavailability of intrinsic food iron. In effect, EDTA acts as a shuttle, protecting iron in the stomach from inhibitory dietary ligands, such as phytates and polyphenols, and releasing it in the duodenum, where it is absorbed [2].

Interactions of NaFeEDTA with inhibitors and enhancers of iron absorption

Phytates, which are present in many cereal and legume grains, are powerful inhibitors of iron absorption. Some direct evidence of the ability of NaFeEDTA to prevent their action was obtained in an experiment where bran, a rich source of phytates, was shown to reduce the absorption of iron from ferrous sulfate eleven-fold [9]. In contrast, no such inhibition occurred when bran was fed with NaFeEDTA. The EDTA was, thus, capable of protecting the iron by holding it in a bioavailable form and preventing its binding to phytate. In contrast, when NaFeEDTA was given with tea, a seven-fold reduction in iron absorption was noted in one study, [9] while in another, tea reduced iron absorption from 11.5% to 1.86%, when it was drunk with a low-extraction wheat roll fortified with NaFeEDTA [14]. These findings indicate that polyphenols have a greater affinity for iron than does EDTA in the conditions existing in the upper gastrointestinal tract. The complexity of these metal-ligand interactions, depending as they do on such factors as molar ratios and pH, is underlined by the *in vitro* observation that EDTA can bind iron and prevent it from forming complexes with tannic acid [15]. Moreover, it is capable of displacing iron from an iron-tannic acid complex. EDTA's protective effect on iron absorption is a partial one, even in the presence of phytates, since absorption has been found to be significantly lower when NaFeEDTA has been fed with high extraction bread rolls (3.9%), than when fed with low extraction ones (11.5%) [14].

The major promoter of iron absorption in the diet is ascorbic acid and, when added to a meal, it produces a dose-dependent increase in iron absorption [16–18]. When, however, NaFeEDTA and ascorbic acid are added together, the enhancing effect is very blunted, only becoming apparent with high doses (100 mg) [9]. Similar findings have been noted with meat, another enhancer of non-heme iron absorption. When NaFeEDTA has been added to meals containing meat, NaFeEDTA has had little or no enhancing effect on non-heme iron absorption [19, 20].

These experiments suggest that NaFeEDTA protects the iron in food from the inhibitory effects of phytate but that it has little effect when stronger inhibitors, such as polyphenols, are present in sufficient concentration. Furthermore, it has little or no enhancing effect in the presence of absorption enhancers, such as ascorbic acid and meat. It would, therefore, not be expected to offer any advantages as a fortificant in diets of high bioavailability.

Iron absorption from foods fortified with NaFeEDTA

A number of human studies have been carried out in which the bioavailability of iron from foods fortified with either ferrous sulfate or NaFeEDTA has been compared. A similar protocol was used in the majority of these studies. It involved the addition of radioiron (^{55}Fe or ^{59}Fe) to the test meal, which was fed on two consecutive days. The relative absorption of the two isotopes was then measured in a blood sample taken two weeks later. Each subject's absorbing capacity was subsequently assessed by measuring the absorption of a reference dose of 3 mg $^{59}FeSO_4 7H_2O$ fed together with 30 mg ascorbic acid. This made it possible to standardize all individual food absorption values to a reference absorption of 40%, a value assumed to represent borderline iron deficiency [21]. In some recent studies, stable isotopes have been used instead of radioisotopes [22, 23].

The results of these various studies are shown in Table I. Absorption of iron from NaFeEDTA was between 2.1 and 3.9 times greater than from with ferrous sulfate when it was fed together with a variety of cereals eaten singly [1, 2, 9, 12–14, 23–29]. The advantage can be ascribed to its capacity to prevent iron from binding with the phytates, which are present in high concentrations in cereals and legumes. These findings with cereals have recently been confirmed and extended [14]. It was shown that iron absorption in human adults was two- to four-fold higher when NaFeEDTA was added to infant cereal, wheat-soy infant cereal, quinoa infant cereal, wheat-soybean cereal, a low-extraction wheat bread roll, and a high-extraction wheat bread roll. A similar enhancement in iron absorption was noted when several "inhibitory"vegetable meals containing phytates and polyphenols were fed (Table I). As discussed previously, the advantage of NaFeEDTA with such diets relates not only to the enhanced absorption of the iron in the fortificant but also to a similar enhancement of all the intrinsic food iron entering the common pool [2]. Insofar as less inhibitory foods, such as milk, potato, and sweet manioc were concerned, there was little enhancement of iron absorption with NaFeEDTA; absorption was even reduced when NaFeEDTA was fed with a neutral food, such as sugar cane syrup. Similarly, in a recent study in which NaFeEDTA was added to a rice and vegetable meal with a low phytic acid content, iron absorption was the same as that obtained when ferrous sulfate was the fortificant [30]. Furthermore, when meat was present in a meal, there was little or no enhancement of iron absorption with NaFeEDTA [19, 20].

Effect of Na_2EDTA on iron absorption

Na_2EDTA is widely used in the food industry as a sequestering agent to prevent oxidative damage by free metals. As discussed in a previous section, Na_2EDTA readily chelates iron in the stomach to form NaFeEDTA. Its effect on iron absorption is, therefore, of interest. In one study, Na_2EDTA and an equimolar amount of iron as ferrous sulfate were added to Egyptian flat bread with a high phytate content [25]. Absorption of iron was 2.6-fold greater than it was when ferrous sulfate was added alone (Table I). These findings show that the same enhancing effects on iron absorption can be obtained in an inhibitory meal when Na_2EDTA and a soluble iron salt are added instead of NaFeEDTA.

The effects of Na_2EDTA on iron absorption are influenced by the molar ratio of EDTA to iron. Earlier work suggested that iron absorption dropped progressively as the EDTA:Fe ratio increased [31]. These observations have been extended in three more recent studies. In the one, a series of experiments was done in which increasing amounts of Na_2EDTA were added to a rice meal fortified with ferrous sulfate [26]. Absorption was significantly increased when the EDTA:Fe ratios were between 1:4 and 1:1, with the maximum absorption (± 3-fold increase) occurring at a ratio of 1:2. Ratios between 2:1 and 4:1 had no significant effect on iron absorption. In a second study, Na_2EDTA up to a molar ratio (EDTA:Fe) of 1:1 was added to ferrous sulfate-fortified wheat cereal and wheat-soybean cereal [14]. The geometric mean absorption of iron from the wheat cereal increased from 1.0% to a maximum of 5.7% at a molar ratio of 2:3, while absorption from the wheat-soybean cereal increased from 0.17% to a maximum of 2.9% at a molar ratio of 1.0. In another recent study, Na_2EDTA was added in differing molar ratios (0.3:1, 0.6:1, and 1:1) to a fortified meal (14 mg Fe as ferrous sulfate) of wheat bread and a drink containing cereal, milk, and soy [32]. The enhancing effect of Na_2EDTA was similar at all three ratios. Na_2EDTA and ascorbic acid did not differ in their enhancing effect at molar ratios of 0.7:1 and 0.6:1 respectively. These various findings suggest that a ratio of EDTA:Fe for iron fortification purposes should probably be in the range of 1:2 to 1:1.

Table 1: Iron absorption from meals fortified with ferrous sulfate or NaFeEDTA (Adapted from Hallberg [19], Bothwell and MacPhail [1], INACG [2], and Hurrell [24])

	Standardized Iron Absorption			
	A	B	B/A	
Meal Components	Ferrous Sulfate	NaFeEDTA	Ratio	Authors
Cereals				
Wheat	6.2	14.6	2.3	Martinez-Torres *et al* [13]
Egyptian flat bread[b]	2.1	5.3	2.7	El Guindi *et al* [25]
Maize meal	4.0	8.2	2.1	MacPhail *et al* [9]
Rice	3.6	10.2	2.8	MacPhail *et al* [26]
Wheat infant cereal	2.2	5.2	2.9	Hurrell *et al* [14]
High extraction white bread	1.0	3.9	3.9	Hurrell *et al* [14]
Maize porridge	1.7	5.7	3.4	Mendoza *et al* [27]
Inhibitory Meals				
Beans, maize, coffee	2.0	5.3	2.7	Viteri *et al* [28]
Beans, plantain, rice, maize, soy[c]	3.1	7.0	2.3	Layrisse & Martinez-Torres [12]
Corn tortillas, black bean paste[d]	5.5	9.0	1.6	Davidsson *et al* [23]
Less inhibitory or 'neutral' foods				
Milk	10.2	16.8	1.6	Layrisse & Martinez-Torres [12]
Potato	5.9	7.3	1.2	Lamparelli *et al* [29]
Sweet manioc	14.1	10.6	1.2	Martinez-Torres *et al* [13]
Sugar cane syrup[c]	33.1	10.8	0.3	Martinez-Torres *et al* [13]
Meat, beans, plantain, rice, maize and soy	4.2	7.4	1.4	Layrisse & Martinez-Torres [12]
Hamburger, string beans and potato	6.2	6.5	1.1	Hallberg [19]

[a] Absorptions standardized to a reference dose (3 mg ferrous sulfate + 30 mg ascorbic acid) absorption of 40%.
[b] A mixture of ferrous sulfate and Na_2EDTA were used in this study.
[c] Comparison between ferrous sulfate and NaFeEDTA not in the same individuals.
[d] Stable isotopic measurements not standardized to a reference dose of 40%.

The studies showing the enhancing effect of Na_2EDTA on iron absorption have been done using ferrous sulfate. Were, however, Na_2EDTA to be considered as a practical agent for enhancing iron absorption, ferrous sulfate would in many circumstances not be a good source of iron because of its propensity to cause organoleptic changes in the vehicles in which it is stored. The little evidence that has been produced thus far suggests that the enhancing effects of Na_2EDTA on iron absorption from food may only occur in the presence of iron salts that are freely soluble in water. In this context, Na_2EDTA was shown to have no enhancing effect on iron absorption when added to a meal based on corn tortillas and black bean paste, which was fortified with ferrous fumarate, an iron salt which is poorly water-soluble but soluble in dilute acid [23]. The lack of effect may relate to the solubility of this compound in gastric juice and complex formation between the EDTA moiety and other minerals and trace elements in the meal. While it is possible that the high pH of the lime-treated corn may have negatively affected the formation of a complex between iron and EDTA, this latter possibility seems unlikely, since Na_2EDTA enhanced iron absorption from the same meal when fortification iron was present as ferrous sulfate. In any event, these important findings with ferrous fumarate require confirmation with other meals, since this iron salt is an attractive fortification option. It causes far fewer organoleptic problems than freely water-soluble compounds but still readily enters the common non-heme iron pool during the digestion of food [24]. The effects of Na_2EDTA on the absorption of another commonly used fortificant, hydrogen-reduced iron, have also been studied in non-anemic female volunteers, using the stable isotope, ^{58}Fe, and the stool recovery method [22]. No enhancement was noted with Na_2EDTA. It should, however, be noted that the basal geometric mean absorption (14.1%) from a meal composed of cornflakes, skimmed milk, and tea was surprisingly high.

In summary, while Na_2EDTA remains an attractive, potential option as an enhancer of iron absorption, the situations in which it could be profitably deployed have not yet been fully explored. Theoretically, it could be used on its own if the dietary iron intake was adequate and the major problem was the presence of an excess of inhibitors. It would also seem to be an option when added with ferrous sulfate to bakery flours that are only stored for short periods. What has still to be identified is an iron source that does not cause organoleptic problems on prolonged storage, and that is also susceptible to the enhancing effects of Na_2EDTA.

Results of intervention trials with NaFeEDTA

Thus far, four fortification trials using NaFeEDTA have been fully reported, while the results of another are available in abstract form. The findings in these various trials will be reviewed briefly.

NaFeEDTA-fortified fish sauce (10–15 mg Fe/day) in Thailand

This fortificant was provided to a Thai village for one year [33]. Packed cell volume (PCV) values showed a significant increase as compared with a control village supplied with unfortified fish sauce. The largest mean change of + 4.6 was seen in a sub-group of women who were anemic at the start of the study. This change was calculated to be equivalent to an increase in body iron of about 190 mg, which represented an increase in iron absorption of 0.5 mg daily.

NaFeEDTA-fortified sugar (± 4.3 mg Fe/day) in Guatemala

The fortified sugar was administered to three out of four Guatemalan communities for 32 months [34, 35]. All pregnant women and subjects with severe anemia received iron therapy or supplements and were excluded from the analysis. Interpretation of the findings was complicated by certain confounding factors, including differences in the initial iron status of the communities, distribution problems, and variations in compliance. Despite these drawbacks, iron stores in the fortified communities increased significantly, except for women aged 18 to 48 years, in one community, and greater than 49 years in another. In addition, children in two of the communities showed a significant improvement in hemoglobin concentrations when compared with children in the control community.

NaFeEDTA-fortified curry powder (± 7.7 mg Fe/day) in South Africa

The fortified curry powder was administered for two years in an Indian community living in Durban, South Africa [36, 37]. It was universally consumed by the Indian population, most of it was obtained from one supplier, and it tolerated well the addition of NaFeEDTA.

The trial was double-blinded and was conducted in a single community, with the 263 families randomly assigned to control and test groups, which were matched for iron status. Care was taken to ensure that crossover between groups did not occur and the curry powder, fortified or unfortified, was distributed directly to each family. In addition to evaluating the usual monitors of improving iron status (increasing hematocrit or hemoglobin and ferritin), an attempt was made to estimate the total body iron in each individual by using a composite of the hemoglobin concentration, percent transferrin saturation, and the serum ferritin concentration [38]. This comprehensive index of iron nutrition made it possible to compare subjects with wide variations in iron status and thus to assess both the beneficial and potentially adverse effects of additional iron, i.e. development of iron overload [37].

A significant improvement in body iron as assessed by the index was detectable in the group of women receiving fortified curry powder after one year of the program. This improvement continued during the second year, when the rise in hemoglobin concentration became significantly greater than that in the control group. The prevalence of iron deficiency dropped dramatically in the women receiving fortified masala. Iron deficiency anemia was detected in 22% of individuals at the start of the study but only in 4.9% after two years of fortification. The most significant improvement in iron status was noted in women who entered the trial with iron deficiency and especially in those with anemia. Those with anemia showed an increase in calculated body iron of 505 mg, which is equivalent to the absorption of an additional 0.7 mg iron/day. The latter figure is close to the predicted improvement in iron balance of 0.8 mg/day based on radioisotope absorption studies using NaFeEDTA-fortified curry powder [29].

In iron-replete males the rise in calculated body iron was modest and reached statistical significance only in alcohol abusers receiving fortified masala. This suggests that iron-replete males are unlikely to accumulate excessive amounts of iron under these fortification conditions.

NaFeEDTA-fortified fish sauce (10 mg Fe/day) in Vietnam

Fortified fish sauce (10 mg Fe/day) was used as the vehicle in a randomized double-blind trial in 152 anemic (Hb 80–119 g/L) women, working in garment factories in Vietnam [39]. Participants were fed a meal based on noodles or rice and 10 mL fish sauce, containing either 10 mg iron as NaFeEDTA or no added iron, for 6 days a week. After 6 months, the geometric mean hemoglobin level was higher (116.3 g/L) in the group receiving iron than in the control group (107.6 g/L), while the prevalence of anemia in the fortified group was 20.3% as compared with 58.3% in the control group.

NaFeEDTA-fortified soy sauce (4 mg Fe/day) in China
Fortified soy sauce is the vehicle being used in an ongoing effectiveness study in China, which is being carried out by Dr. Junshi Chen and colleagues [40]. Soy sauce was selected as the food carrier because about 70% of the population in China consumes soy sauce, and NaFeEDTA was selected as the iron compound because of its high bioavailability for people consuming a plant-based diet. In preliminary studies in adult Chinese women, the average percentage iron absorption from soy sauce fortified with either NaFeEDTA or $FeSO_4$ in soy sauce was found to be 10.5 and 4.7% respectively. Furthermore, soy sauce containing 5 or 20 mg Fe, as NaFeEDTA, was found to be highly effective in the treatment of anemic children within 3 months.

A double-blind, controlled effectiveness trial, using NaFeEDTA-fortified soy sauce, was started in September 2000, covering approximately 10000 subjects in a high-risk population, with a 30% prevalence of anemia. After six months, there was a highly significant increase in hemoglobin levels and a reduction in the anemia prevalence rate of ± 50% for all age groups in the group receiving the iron-fortified sauce. In contrast, there were no significant changes in the control group. The trial was scheduled to continue for two years.

Specific Issues Relating to the Use of NaFeEDTA as an Iron Fortificant

The results of several fortification trials, reviewed in the previous section, suggest that NaFeEDTA shows real promise as an iron fortificant, especially in developing countries, where the cereal- or legume-based diets contain large amounts of inhibitors of iron absorption. Before it is recommended for widespread use, however, there are a number of issues that must be addressed. They include (a) its potential direct toxicity, (b) possible interactions between EDTA and other dietary minerals, (c) the potential of NaFeEDTA to induce iron overload, (d) technical issues relating to the use of NaFeEDTA, (e) regulatory issues, (f) cost considerations, and finally, (g) potential target populations. These issues will be considered separately.

Toxicity of EDTA-metal complexes

As previously discussed, NaFeEDTA, like other EDTA-metal complexes, dissociates in the gut to a bioavailable form of iron and an EDTA salt. The subsequent fate of the iron and the EDTA are independent of each other, with almost all the EDTA being passed out unchanged in the stool [8]. Because of the dissociation occurring in the gut, data obtained with other EDTA-metal complexes, such as $CaNa_2EDTA$ and Na_2EDTA, are equally relevant when considering the safety of NaFeEDTA [2, 21]. Evidence related to the potential toxicity of EDTA-metal complexes was reviewed in detail by the International Nutritional Anemia Consultative Group in 1993 and by Heimbach and coworkers in 2000 [2, 41]. In summary, NaFeEDTA has a degree of acute oral toxicity similar to that of ferrous sulfate [42] and EDTA-metal complexes are not reproductive or developmental toxicants when fed with a nutrient-sufficient diet or minimal diets supplemented with zinc. In chronic toxicity studies, diets containing as much as 5% EDTA did not produce toxic effects. EDTA compounds are not carcinogenic in experimental bioassays and are not directly genotoxic. In this latter context, NaFeEDTA, like other iron salts, was not mutagenic in the Ames *Salmonella* assay but did cause a mild increase in mutants when added at high concentrations to a mouse lymphoma assay [43]. Similar findings were noted with ferrous sulfate and other iron compounds.

The lack of significant toxicity of EDTA compounds is consistent with a history of safe use of $CaNa_2EDTA$ and Na_2EDTA as preservatives, processing aids, and color stabilizers in many foods at an ADI of 2.5 mg EDTA/kg/day for a number of years.

Possible interactions of EDTA with other dietary minerals

The potential impact of EDTA present in NaFeEDTA (10 mg Fe/day) on nutritional status with respect to other dietary minerals can be calculated, assuming that each mineral is present in an amount equivalent to its recommended dietary allowance (RDA) [2, 6]. Relevant figures are 2 mg for copper, 15 mg for zinc, 350 mg for magnesium, and 800 mg for calcium. On a molar ratio basis, there is 50 times more magnesium and 80 times more calcium than EDTA, which suggests that EDTA would be unlikely to have any effect on the metabolism of either metal. In contrast, copper and zinc could be affected, since, on a molar basis, there is 8 times more EDTA than copper and equivalent amounts of zinc. The actual effects of EDTA on mineral metabolism have been measured in several studies. Increasing levels of EDTA in the diet of rats increased zinc absorption and to a lesser extent also increased copper absorption, but had no effect on calcium absorption [2, 44]. Zinc absorption was increased from 20% with ferrous sulfate to 34% with NaFeEDTA [44]. Urinary zinc excretion was also increased from 0.3 to 0.6% in women but this had little or no effect on overall zinc metabolism [45]. It was therefore apparent that the EDTA moiety from added NaFeEDTA increases both iron and zinc absorption from meals containing phytates and it is possible that it also causes an increase in the absorption of copper. Further information on the possible effects of NaFeEDTA fortification on zinc metabolism was obtained in two trials, which lasted for 20 and 24 months respectively [37, 46]. No changes in serum zinc levels were noted over the period of the trials.

Of concern is EDTA's possible effect on the absorption of potentially toxic elements, such as lead, cadmium, mercury, aluminum, and manganese. The limited studies, which have been reported, have not shown adverse effects. In one study in mice, the effects of a number of factors on the absorption of lead were measured [47]. Absorption of the lead was increased in the presence of citrate and orange juice but EDTA had no effect. In a more recent study in rats fed a high-iron diet (140 mg/kg/day), iron accumulation in the body at 32 and 61 days was no higher with NaFeEDTA as the iron source than it was with $FeSO_4$ [48]. In a third study, 100 μg ^{203}Pb was fed to 85 subjects, with approximately 60% being retained in the body [49]. Ascorbic acid slightly lowered lead retention, while EDTA produced a marked reduction. In another study in humans, several agents were administered together with 0.27 mol ^{203}Pb [50]. When 3 (mol EDTA was added, retention of lead in the body was reduced from a mean of 56.8% to 8%. Of possible relevance to these various findings is the fact that intravenous EDTA has been used for a number of years as a therapy for both acute and chronic lead poisoning [51]. In relation to other toxic metals, the effects of EDTA on cadmium absorption were studied in acute toxicity experiments in mice [52]. Mortality was reduced from over 90% to zero and body retention of cadmium was somewhat less when administered with EDTA. In a final study, manganese absorption and urinary excretion were studied in adults after the administration of a weaning cereal fortified with either NaFeEDTA or ferrous sulfate [53]. No significant differences in absorption and excretion were found.

Potential of NaFeEDTA fortification to lead to iron overload

There is a close inverse relationship between body iron stores and non-heme iron absorption [54] and this relationship remains unchanged when NaFeEDTA is used as the iron source [20]. This is not surprising, since there is a good deal of evidence that iron ingested as NaFeEDTA equilibrates with the common pool of non-heme iron in food [2] and, as part of that pool, its absorption is influenced by the same factors that control iron balance. At the same time, more general questions have been raised relating to the possible long-term effects of effective iron fortification programs on iron-replete adult males [55]. At present, evidence in this regard is inconclusive. A comparison of longitudinal survey data obtained in the NHANES II study (1976–1980) with pilot data from the NHANES III study (1987–1988) suggested that serum ferritin levels may have risen [56]. When the effects of iron fortification have been studied more directly, however, limited evidence has been obtained which suggests that control mechanisms remain effective with small increments in dietary iron intake. In one study, an adult male with normal stores was given 10 mg iron daily as ferrous sulfate for 500 days without any significant change occurring in the serum ferritin level [57]. Similar results were noted in a fortification trial, summarized in a previous section, in which NaFeEDTA was added to curry powder to provide approximately 7.5 mg extra dietary iron per day over a two-year period [37]. Although the prevalence of anemia in women dropped dramatically, there was no significant rise in serum ferritin levels in males who were over the age of 18 years and whose iron status was normal at the beginning of the study.

The degree to which effective iron fortification might be expected to affect phenotypic expression in individuals with a genetic predisposition to absorb iron excessively has been the subject of debate [55]. The two situations, which are of most relevance in this regard, are hereditary hemochromatosis, a disorder most commonly associated with mutations in an HLA-linked gene, *HFE*, and iron-loading anemias, such as thalassemia major [58]. The frequency of heterozygotes for the *HFE* mutation in populations of European origin ranges between 8 to 18%, indicating that between 0.16 and 1.0% are homozygotes. It is, therefore, apparent that the hemochromatosis gene is one of the most common disease-producing genes in Caucasoids. However, the frequency with which homozygotes show clinical disease, with morbidity and mortality, has recently been questioned [58]. While family studies have shown that the majority of affected homozygotes express the disease, necropsy studies suggest that hereditary hemochromatosis is a rare clinical disorder [58, 59]. This latter view has recently been supported by an epidemiologic study in the USA, in which 41,038 subjects attending a health appraisal clinic were tested for *HFE* mutations [60]. Only one of the 152 subjects diagnosed as homozygous had signs and symptoms suggestive of hemochromatosis. While clinical expression may vary in different Caucasoid populations, these findings do suggest that effective iron fortification, such as that provided by NaFeEDTA, might be expected to lead to an increased rate of iron accumulation only in that very small proportion of subjects, homozygous for the *HFE* mutation, who already have a propensity to absorb iron excessively.

The *HFE* mutation is absent in Asian and African populations [58] and iron loading, when it occurs, is almost always associated with hematologic disorders, such as thalassemia. These conditions have, however, less direct relevance to iron nutritional programs, since affected homozygotes are identified clinically at an early age and, in any event, are optimally maintained on blood transfusions, which in themselves load the body with massive amounts of iron [61].

The question arises whether the homeostatic controls that control iron balance can be overcome by even larger amounts of dietary iron than are provided by iron fortification. In this context, the situation in sub-Saharan Africa is of interest. Iron overload is common in the region and has been ascribed to the lifetime consumption of alcoholic drinks, home-brewed in iron containers [62]. As a result, daily intakes of up to 100 mg may occur [54, 62]. Current evidence, however, derived from pedigree studies, suggests that iron overload only occurs in individuals with a genetic predisposition, the exact nature of which has not yet been defined [63].

There is one final pertinent point related to the possible use of NaFeEDTA as a fortificant in populations consuming "Western-type"diets containing adequate amounts of meat and ascorbic acid. NaFeEDTA has no enhancing effect on iron absorption when added to such diets and its increased cost in relation to a number of other iron fortificants largely precludes its use under such circumstances. In contrast, it is an attractive option in iron-deficient populations subsisting on diets with a high content of inhibitors of iron absorption.

Technical considerations relating to the use of NaFeEDTA

There are a number of technical issues related to the use of NaFeEDTA as an iron fortificant. They relate, on the one hand, to the stability of the complex in a number of vehicles during processing, storage, and cooking and, on the other, to consumer acceptance of the fortified food in relation to its physical, organoleptic, and chemical properties. At the outset, it must be stated that evidence in this regard is patchy and incomplete.

NaFeEDTA, which is pale yellow in color, causes fewer organoleptic problems than other water-soluble iron compounds. Its suitability for addition to a number of potential vehicles is considered here:

Cereals: Cereal flours are currently the most frequently used vehicles for iron fortification. For organoleptic reasons, wheat and maize are usually fortified with elemental powders and rice with ferric pyrophosphate [24]. Only bread, wheat flour stored for less than three months, and pasta, with its low moisture content, can be fortified with the more highly available ferrous sulfate [64]. NaFeEDTA, on the other hand, has the advantage that it does not provoke the fat oxidation reactions in wheat flour that lead to rancid oxidized products. For example, wheat flour-stored for six months at 37ºC underwent little fat oxidation, whether or not it was fortified with NaFeEDTA [24]. Questions have, however, been raised concerning the dough viscosity and specific volume of bread made from flour fortified with NaFeEDTA [65].

Breakfast cereals, including corn flakes and other ready-to-eat cereals, were marketed in Latin America by the Kellogg Company for a short period. NaFeEDTA has also been recommended as a fortificant in nixtamalized corn flour, which has a high content of inhibitors of iron absorption, "provided there are no sensory problems" [66]. In this context, consumer tests carried out by the Council for Scientific and Industrial Research in South Africa on corn (maize) meal and wheat flour fortified with NaFeEDTA (18 mg Fe/kg), revealed color and taste differences in the fortified cooked products (porridge and bread) [67]. In contrast, it is encouraging to note that maize meal fortified with NaFeEDTA (20 mg Fe/kg) is being successfully marketed in Kenya [68].

The technology also exists for the fortification of whole grains, such as *rice*, but this approach does not seem to have been explored with NaFeEDTA. Current constraints on rice fortification relate to cost and difficulties in masking fortified grains [24].

Sugar has been successfully fortified with several different ferrous and ferric compounds together with ascorbic acid [69]. There were, however, unacceptable color reactions when added to coffee and tea [69] and to certain maize products [35]. NaFeEDTA (13 mg Fe/kg sugar) was used in an extended and successful fortification program in Guatemala [34, 35]. It does, however, cause a slight color change in the appearance of the sugar and darkens both tea and coffee, presumably due to the formation of complexes with tannins.

Salt has not been used as a vehicle for NaFeEDTA fortification in any published studies. Experience with other iron salts suggests that color changes may present a problem, especially in the crude salts used in many developing countries [24].

Milk has potential as a vehicle for iron fortification with NaFeEDTA but possible organoleptic problems have not been extensively investigated. It would, however, be expected to cause unwanted color changes when added to tea, coffee, or cocoa. Similarly, NaFeEDTA has been found to be unsuitable for the fortification of chocolate drink powders and infant cereals containing banana and other fruits [24]. In addition, when added to cornstarch puddings and gruels, the foods turn a pinkish, violet color [24].

Condiments that are traditionally used in developing countries have been shown to be extremely promising vehicles for fortification with NaFeEDTA. Pilot fortification trials have been carried out with fish sauce [33, 39] curry powder [37], and soy sauce [40] and each has reported success. In addition, the flavor enhancer, monosodium glutamate, has been successfully fortified with other salts of iron [70], but not yet with NaFeEDTA. The evidence available thus far suggests that organoleptic problems may not be a major problem with these various condiments. Consumer acceptance seems to have been good in the various trials that have been undertaken, while the formal testing that has been carried out has indicated stability of the fortified vehicles. For example, unlike many other soluble iron compounds, NaFeEDTA does not cause precipitation of peptides when added to fish or soy sauce [71]. In this context, soy sauce has recently been marketed commercially in the Far East. [68]. Curry powder also seems to be a stable vehicle. Being highly colored and spiced, it tolerates well the addition of NaFeEDTA and, because it is slightly sticky, there is no tendency for the NaFeEDTA to sediment out of the curry powder [29]. The powder has been shown to remain stable over several months of storage and consumer acceptability, based on an analysis of questionnaires, has been high in terms of appearance and taste.

While the few data available on the technical aspects of fortifying condiments with NaFeEDTA are promising, more formal testing has raised certain important technical issues. NaFeEDTA is stable at cooking temperatures of 100°C but processing fortified food at significantly higher temperatures may cause problems [72]. In addition, NaFeEDTA in liquid products can be degraded by ultraviolet rays from sunlight, with losses of EDTA of up to 35% occurring in fortified fish sauce stored for six to eight weeks in clear bottles in the sunlight [73]. Such losses were not noted with soy sauce, which is much darker in color, and could be prevented by storing fish sauce in dark bottles or in artificial light.

Regulatory issues related to the use of NaFeEDTA

With so much evidence suggesting that NaFeEDTA is a potentially effective food fortificant, it is important to examine the nature of the constraints that have limited its more widespread use. In 1974, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated $CaNa_2EDTA$ and Na_2EDTA as food additives. Based on animal toxicology studies JECFA allocated an ADI of 2.5 mg EDTA/kg body weight/day. Since that time they have been used extensively in a wide variety of foods as preservatives, processing aids, and color stabilizers. [41, 74]. In the USA, $CaNa_2EDTA$ is recognized by the Food and Drug Administration (FDA) as a direct food additive approved for use in foods such as carbonated soft drinks, canned cooked vegetables, potato salad, frozen white potatoes, mayonnaise, salad dressings, margarine, sandwich spreads, and canned cooked shellfish, at concentrations ranging from 25 to 800 ppm. Na_2EDTA is also recognized by the FDA as a direct food additive approved for use in a similar variety of food products and in aqueous multivitamin preparations at concentrations ranging from 36 to 500 ppm [41, 74]. While these two salts of EDTA may be added to 34 different products in the USA, it is of interest that the actual consumption has been estimated not to exceed 0.25 mg EDTA/kg day/day, which is ten times less than the ADI of 2.5 mg EDTA/kg day/day [75]. Refinements of this analysis, together with production figures for food-grade EDTA, suggest even lower intake figures [41]. While other countries, such as Malaysia and the Philippines, also allow EDTA in a wide range of foods, the European Economic Community takes a more restrictive view and only allows its addition to canned crabs, canned shrimp, pickles, canned mushrooms, glacé cherries, and sauces. It should be noted that the FDA approves neither Na_2EDTA nor $CaNa_2EDTA$ for use in infant formulas.

In contrast to other salts of EDTA, NaFeEDTA is not currently recognized by the FDA as a direct food additive. In 1993, JECFA evaluated NaFeEDTA for use in supervised food fortification programs in populations in which iron-deficiency anemia is endemic and provisionally concluded it was suitable for such an application [76]. At the time, however, JECFA requested further animal toxicological data. This decision was surprising since, as previously discussed, it can be predicted from the chemical properties of EDTA complexes that the EDTA moiety of NaFeEDTA consumed with food behaves similarly to the EDTA moiety from $CaNa_2EDTA$ or Na_2EDTA [2]. The EDTA moiety forms similar complexes in the digestive tract, irrespective of whether it is fed as $CaNa_2EDTA$, Na_2EDTA, or NaFeEDTA, with the EDTA having the same fate [2]. In any event, JECFA reviewed additional data on NaFeEDTA in 1999 and removed the "provisional"qualification from its previous decision. It concluded "that sodium iron EDTA could be considered safe when used in supervised fortification programs" [5]. It should, however, be noted that JECFA is not a regulatory body and no petitions for the use of NaFeEDTA as a direct food additive have yet been submitted to the regulatory authorities in the USA nor has anyone submitted a Generally Recognized as Safe (GRAS) notice to the FDA regarding NaFeEDTA.[1]

1 GRAS substances are exempt from pre-market approval by FDA. Under Section 201 (s) of the FFDCA, a substance is

Heimbach and coworkers have calculated what possible extra impact the use of NaFeEDTA as a fortificant in the USA would have on total dietary EDTA intake if it were added at maximum intended concentrations (20% of the daily value for iron) in all brands and all product lines of ready-to-eat cereals, toasted pastries, breakfast bars, and granola bars [41]. The estimated daily intakes (EDIs) of EDTA at the 90th percentile from current plus intended uses would be 1.15 EDTA/kg body weight/day for the whole US population and 2.06 mg EDTA/kg body weight/day for children aged 1–6 years. These numbers correspond to 46% and 82% of the ADI (2.5 mg EDTA/kg body weight/day) respectively. In light of this, the fortification of infant milk and cereal formulas with NaFeEDTA does not seem appropriate, since the amounts of NaFeEDTA required to deliver sufficient fortification iron would approach the ADI of 2.5 mg EDTA/kg body weight/day.

Cost considerations

While NaFeEDTA is currently six to eight times more expensive than ferrous sulfate, it is two to three times better absorbed than water-soluble fortificants from diets containing large amounts of inhibitors of iron absorption, which means that lesser amounts of fortificant can be added [24, 65, 66]. In addition, ascorbic acid, which is relatively expensive, does not need to be added as an absorption enhancer [24]. Additional savings can be made in the packaging, since less sophisticated packaging material can be used for food fortified with NaFeEDTA than for food fortified with ferrous sulfate or other iron salts and ascorbic acid. The better packaging material must be designed to protect ascorbic acid from degradation during storage [24]. Despite these considerations, there is currently a real need for food-grade NaFeEDTA to become more widely available and affordable. In this context, it seems entirely possible that the cost will drop if there is a large demand for fortification-grade NaFeEDTA. One final point to bear in mind is the expectation that an effective fortification program would, after several years, reduce the costs of current supplementation and therapeutic programs for the control of iron deficiency [34].

Alternative strategies might include the use of Na_2EDTA alone as a means of enhancing the absorption of the intrinsic food iron in inhibitory diets [14]. Alternatively, it could be administered in an EDTA:Fe molar ratio of between 1:2 and 1:1 with another iron source. The results of one study in which radioisotopes were used to measure iron absorption from Egyptian flat breads [25] suggests that the approach could prove successful if Na_2EDTA and ferrous sulfate were added to bakery flours, which are stored for short periods. The search continues for an iron source that does not cause organoleptic problems and with which NaFeEDTA also enhances the absorption.

exempt from the definition of food additive (and therefore exempt from the requirement of pre-market approval), if its safety is generally recognized under intended conditions of use by qualified experts. FDA has a voluntary GRAS notification program whereby anyone may inform FDA of their opinion that their intended use of an ingredient is generally recognized as safe.

Potential target populations

Fortification with NaFeEDTA can be expected to be most efficacious in iron-deficient populations subsisting on diets based on cereals and legumes, such as whole-wheat flour, corn meal, soybean, and other legume products. These diets have a high content of the major inhibitors of iron absorption (phytates and polyphenols) and a low content of enhancers (ascorbic acid and meat). In contrast, NaFeEDTA offers no real advantages as an iron fortificant in populations consuming mixed 'Western-type' diets containing adequate amounts of meat and ascorbic acid.

While NaFeEDTA seems well suited for use as an iron fortificant in developing countries, there are a number of constraints impeding its widespread use. These include its relatively high cost, difficulties in identifying suitable vehicles, distribution problems, and regulatory issues. None of these is, however, insurmountable. As previously discussed, the high cost is offset to some degree by the higher bioavailability, so that it might be possible to reduce the daily fortification amount from 10 mg Fe to 5 mg Fe. In addition, the costs of food-grade NaFeEDTA will almost certainly drop if it is used widely as a fortificant.

The most obvious vehicles for NaFeEDTA fortification in developing countries are cereals, such as wheat flour, corn meal, and rice, which are the staple foodstuffs in many populations. While complete organoleptic profiles on each of them may not have been carried out, wheat flour has been shown to tolerate well fortification with NaFeEDTA [24], and several breakfast cereals fortified with NaFeEDTA were marketed for a short time by the Kellogg Company in Latin America. These were later withdrawn for undisclosed reasons [77]. In this context, it is of interest that fortified maize meal is currently being marketed in Kenya [68]. However, no fortification trials using a cereal as the vehicle and NaFeEDTA as the fortificant have yet been published. The identification of other suitable vehicles has, at least partially, been addressed in several fortification trials. One of them used sugar as the vehicle [34, 35] while the others used condiments, including soy sauce [40], fish sauce [33, 39], and curry powder [29, 36, 37]. The studies were designed to supply between 4 and 15 mg extra iron per day and each reported an improvement in the iron status of the target population. The degree to which such trials can be expanded on a regional or national level, as is being planned in China and Vietnam, remains to be seen. As mentioned previously, a constraint on the use of fortified cereals, such as wheat flour and maize flour, is lack of centralized production and distribution and presumably the same applies to condiments, which are obtained from many different sources. When vehicles from a number of sources are fortified, quality control becomes an additional important issue. Finally, the degree to which organoleptic problems and consumer acceptance may limit the widespread use of NaFeEDTA as an iron fortificant is not completely resolved. What is currently lacking is a coherent, standardized body of information, systematically collected, on the technical functionality of NaFeEDTA in widely consumed food vehicles.

In any given population it is infants and women of childbearing age who are the most vulnerable [78] and, as a result, there are targeted programs that are specifically directed at them. These include the fortification of infant milk and cereal formulas with iron and ascorbic acid and supplementation with therapeutic iron in pregnancy [1]. Insofar as infants are concerned, NaFeEDTA does not seem to be a good option, since iron intake relative to body weight is high and the fortification of infant formulas might be expected to be close to the ADI of 2.5 mg EDTA/kg day/day. For example, if a cereal fortified with NaFeEDTA supplied 0.3 mg daily, which is about 30% of the daily absorbed iron requirement of 1 mg in a 10 kg infant, and the absorption of iron from the fortified cereal was 10%, then 3 mg iron (20 mg EDTA) would need to be present in the fortified cereal. This EDTA amount is equivalent to 2.0 mg EDTA/kg day/day.

While the goal of universal fortification in any population may be difficult to realize, there is no reason why more focused programs, targeted at some particular segment of the population, need not be carried out. The fortification trial carried out in South Africa in an Indian population underlines the point [37]. While the prevalence of iron deficiency in Indians was high, they lived in an area where the local black population was iron-replete, with a proportion suffering from African iron overload [62]. In looking for a suitable vehicle for NaFeEDTA, curry powder was chosen, since it was consumed by the Indian population and not by the black population. In the same way, it may be possible to fortify vehicles intended for specific target groups (e.g., cereals prepared for school feeding programs and drinks particularly targeted at teenagers).

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