Revised recommendations for iron fortification of wheat flour and an evaluation of the expected impact of current national wheat flour fortification programs

Richard Hurrell, Peter Ranum, Saskia de Pee, Ralf Biebinger, Lena Hulthen,
Quentin Johnson, and Sean Lynch

Abstract

Background: *Iron fortification of wheat flour is widely used as a strategy to combat iron deficiency.*

Objective: *To review recent efficacy studies and update the guidelines for the iron fortification of wheat flour.*

Methods: *Efficacy studies with a variety of iron-fortified foods were reviewed to determine the minimum daily amounts of additional iron that have been shown to meaningfully improve iron status in children, adolescents, and women of reproductive age. Recommendations were computed by determining the fortification levels needed to provide these additional quantities of iron each day in three different wheat flour consumption patterns. Current wheat flour iron fortification programs in 78 countries were evaluated.*

Results: *When average daily consumption of low-extraction (≤ 0.8% ash) wheat flour is 150 to 300 g, it is recommended to add 20 ppm iron as NaFeEDTA, or 30 ppm as dried ferrous sulfate or ferrous fumarate. If sensory changes or cost limits the use of these compounds, electrolytic iron at 60 ppm is the second choice. Corresponding fortification levels were calculated for wheat flour intakes of < 150 g/day and > 300 g/day. Electrolytic iron is not recommended for flour intakes of < 150 g/day. Encapsulated ferrous sulfate or fumarate can be added at the same concentrations as the non-encapsulated compounds. For high-extraction wheat flour (> 0.8% ash), NaFeEDTA is the only iron compound recommended. Only nine national programs (Argentina, Chile, Egypt, Iran, Jordan, Lebanon, Syria, Turkmenistan, and Uruguay) were judged likely to have a significant positive impact on iron status if coverage is optimized. Most countries use non-recommended, low-bioavailability, atomized, reduced or hydrogen-reduced iron powders.*

Conclusion: *Most current iron fortification programs are likely to be ineffective. Legislation needs updating in many countries so that flour is fortified with adequate levels of the recommended iron compounds.*

Introduction

The World Health Organization (WHO) estimates the global prevalence of anemia to be 47% in children under 5 years of age, 30% in nonpregnant women of childbearing age, and 42% in pregnant women [1]. Prevalence rates are highest in Africa and Asia. WHO does not report prevalence rates for iron deficiency; however, nutritional iron deficiency is the main etiologic factor responsible for anemia in industrialized countries and contributes to about 50% of the anemia in the developing countries of Africa and Asia [2]. Iron deficiency occurs when iron requirements cannot be met by absorption from the diet, such as during periods of rapid growth (infancy, adolescence), in pregnancy, and as a result of menstrual or pathological blood loss. Although physiologic mechanisms can up-regulate iron absorption more than 20-fold from single meals containing readily bioavailable iron [3], the plant-based diets that are characteristic of developing countries limit iron absorption because they are rich in phytate and polyphenols [4, 5]. They also contain little animal tissue, which is a source of highly bioavailable iron. The resultant imbalance between requirements and absorption leads to iron deficiency that, depending on severity, may or may not cause anemia.

The high prevalence of iron deficiency in developing

Richard Hurrell and Ralf Biebinger are affiliated with the Swiss Federal Institute of Technology (ETH), Zurich, Switzerland; Peter Ranum is a consultant for the Micronutrient Initiative, Tucson, Arizona, USA; Saskia de Pee is affiliated with the World Food Programme, Rome, Italy; Lena Hulthen is affiliated with the University of Gothenburg, Sweden; Quentin Johnson is affiliated with the Flour Fortification Initiative, Rockwood, Ontario, Canada; Sean Lynch is affiliated with Eastern Virginia Medical School, Norfolk, Virginia, USA.

Please address inquiries to the corresponding author: Richard Hurrell, Swiss Federal Institute of Technology (ETH), Institute of Food Science and Nutrition, ETH Zentrum; LFV D20, Schmelzbergstrasse 7, 8092 Zürich, Switzerland; e-mail: Richard.hurrell@ilw.agrl.ethz.ch.

countries has a significant adverse impact on the well-being and productivity of their citizens. Physical work capacity is reduced. Iron deficiency in pregnancy contributes to the risk of severe anemia, which is associated with higher maternal morbidity and mortality [6]. There is an increase in the risk of preterm delivery and low birthweight and a higher infant mortality rate [7]. Iron deficiency is also more likely to occur after 4 months of age in babies born to mothers with suboptimal iron status during pregnancy [8]. Iron deficiency in infants and young children is associated with delayed mental and motor development [9]. These children may experience emotional problems and fail to meet educational goals later in life, leading to a negative impact on earning capacity in adulthood. The median total annual productivity loss (physical and cognitive combined) has been estimated to be US$16.78 per capita or 4.05% of GDP [10]. The relationship between iron status and infectious diseases is complex and the subject of considerable debate. However, recent observations indicate that upper respiratory infections are more frequent and last longer and that the risk of severe morbidity related to falciparum malaria is increased in iron-deficient children [11, 12].

Four strategies for alleviating nutritional iron deficiency have been advocated. They are dietary diversification to improve iron bioavailability, selective plant breeding or genetic engineering to increase the iron content or to reduce absorption inhibitors in dietary staples, iron fortification of industrially manufactured foods, and iron supplementation with pharmacological doses, usually without food. Food fortification is regarded at the present time as the safest and most cost-effective approach for populations that consume significant quantities of industrially manufactured foods. Staple foods such as cereal flours and condiments are the most appropriate food vehicles for fortification.

Mass fortification is designed to improve the bioavailable iron intake of the whole population with the intention of eliminating iron deficiency in young children, adolescents, and menstruating women, without causing harm to men and postmenopausal women, who may consume more iron than they require. The efficiency of the physiologic mechanisms for preventing the absorption of unnecessary iron has been questioned, and mandatory wheat flour fortification programs were discontinued in two European countries, in part because of concern about possible adverse effects of iron fortification [13, 14].

The mechanisms controlling iron absorption and the central role of the hepcidin/ferroportin axis have been elucidated recently [15]. There are very few reports of iron overload resulting from the consumption of large quantities of iron, even large supplemental doses, over extended time periods by individuals with an apparently normal hepcidin/ferroportin axis. Systemic iron overload occurs in genetic disorders, such as hemochromatosis, that modify the function of hepcidin or ferroportin, or in diseases, such as the thalassemia syndromes, that reduce the efficiency with which these regulators prevent excessive iron accumulation [16]. Patients with phenotypically expressed iron loading conditions suffer the consequences of excessive iron absorption even if the diet is not fortified, although mass fortification would be expected to modestly increase their iron loads. These disorders are best managed by screening and treatment. Withholding iron fortification from the much larger population that is in need of extra iron would prolong the suffering and the negative health and economic consequences related to iron deficiency and have little impact on the clinical course of the iron overload diseases [17]. Iron overload does not occur in genetic carriers with normal phenotypes [18].

Effective fortification of staple foods or condiments with iron is thus expected to have significant benefits for large segments of the population, particularly in developing countries, with very little risk of adverse health effects. In this respect, wheat flour is the food vehicle most often fortified with iron. Fortification originally began in the United States and Europe in the 1940s as a way to combat iron deficiency by restoring the iron level of low-extraction wheat flour to that in the whole grain. Wheat flour fortification programs are in place or in the planning stages in 78 countries [19]. In 2004, a Centers for Disease Control and Prevention (CDC) expert group in Cuernavaca, Mexico, made global recommendations for the type and level of different iron compounds to be added to wheat flour [20]. WHO [2] recommended the same iron compounds but suggested that each country should estimate the level of fortification that would provide the required iron lacking in the traditional diet.

The first objective of this review was to evaluate and revise the guidelines for iron fortification of wheat flour that were formulated at the Cuernavaca Workshop [20]. This was achieved by reviewing all published efficacy trials of iron-fortified condiments and cereal staples in women and children. For each iron fortificant currently recommended for wheat flour fortification, the average increase in an individual's daily iron intake necessary to achieve a meaningful improvement in iron status was estimated. This information was used to calculate recommended fortification levels based on average per capita wheat flour consumption. The second objective was to evaluate to what extent the flour industry is following the Cuernavaca guidelines and to judge the potential impact of current national, regional, or planned wheat flour fortification programs on the iron status of the population.

Using iron efficacy studies to estimate iron fortification levels that will usefully improve iron status

The iron fortification levels recommended in the Cuernavaca guidelines [20] were largely derived from what was being practiced in the flour fortification industry and what was expected to be organoleptically acceptable. As wheat flour fortification has historically been based on restoration, the iron level recommended for ferrous sulfate fortification (30 ppm iron) was that needed to restore the iron level of low-extraction white wheat flour to that of the whole-grain wheat flour. This was increased to 45 ppm iron for countries where wheat flour consumption was less than 200 g per person per day. Isotopic iron absorption studies in adult humans have indicated that ferrous fumarate has a similar bioavailability to ferrous sulfate, so the Cuernavaca guidelines recommended that ferrous fumarate be added at the same level as ferrous sulfate.

Ferrous fumarate would be expected to have fewer sensory problems than ferrous sulfate. Encapsulation of ferrous sulfate or ferrous fumarate with hydrogenated vegetable oils may prevent lipid oxidation during wheat flour storage, and these compounds are useful alternatives; however, at the time of the Cuernavaca meeting the particle size of the commercially encapsulated compounds was too large, and it was concluded that, if added to flour, the compounds would be removed by the sieves commonly used at the end of the milling process. The Cuernavaca guidelines recommended that smaller particle-size encapsulated ferrous sulfate or encapsulated ferrous fumarate be developed for addition to wheat flour. Although this has been recently accomplished experimentally [21], the microcapsules need more complete sensory testing and scaling up for commercialization. Encapsulated ferrous sulfate and encapsulated ferrous fumarate are recommended for cereal flour fortification in the WHO guidelines [2].

Because elemental iron powders are organoleptically inert, they are widely used for wheat flour fortification. In 2002, a SUSTAIN task force evaluated the usefulness of the different elemental iron powders commonly employed in wheat flour fortification [22]. Based on *in vitro*, rat, and human studies, the task force recommended that electrolytic iron be the only elemental iron powder used and that it be added at twice the iron level of ferrous sulfate, since it is approximately half as well absorbed. They also recommended that carbon monoxide–reduced iron should not be used because of an unacceptably low absorption, and that more studies were needed of carbonyl and hydrogen-reduced iron powders before a recommendation could be made. It was subsequently found that another form of reduced iron (atomized iron powder) is widely used for wheat flour fortification because of its low cost. However, because of its low solubility in dilute acid under standardized conditions and its poor absorption in rat hemoglobin repletion studies and human iron tolerance tests [23], atomized reduced iron powder is not recommended for wheat flour fortification [2].

It has long been known that in the presence of phytate, the ethylenediaminetetraacetate (EDTA) component of NaFeEDTA enhances absorption of both the intrinsic food iron and the fortification iron. Additionally, NaFeEDTA does not promote lipid oxidation in stored wheat flour [24]. It has thus been recommended for the fortification of high-phytate flours (whole-grain and unleavened low-extraction). The level recommended for both whole-grain and unleavened low-extraction flours was 30 ppm iron [20], although it was realized that this level may be somewhat higher than that necessary for high-extraction flours which contain higher levels of (low-bioavailability) intrinsic iron.

The procedure used to determine the recommended iron levels at Cuernavaca was necessarily pragmatic. The preferred procedure would be the method recommended by WHO [2], in which each country must first measure the daily iron intake in the groups at risk for iron deficiency, estimate the iron bioavailability from the diet, compare estimated iron intake and bioavailability with iron requirements (based on dietary iron bioavailability), and calculate the amount of iron lacking in the diet. This amount of iron should then be added to the mean daily flour consumption of the targeted at-risk group(s) (e.g., women of childbearing age). Unfortunately, very few countries have the capability to use this procedure.

The approach used to develop the recommendations in the present document is a combination of the application of experimental evidence and pragmatism. This was made possible by the publication of a relatively large number of human efficacy trials, mostly after the Cuernavaca Workshop. We have reviewed these efficacy studies, in which different iron compounds and different food vehicles were employed. Studies in infants were not included, because this population group is not a primary target for mass fortification. Studies in which ascorbic acid was given together with the fortified food were also excluded, as this iron absorption enhancer is usually unstable to wheat flour storage and heat processing. We also excluded studies where the iron compound was not identified clearly or where the methodological details were inadequate. The duration of the intervention was taken into account. Hallberg et al. [25] estimated that it takes 2 to 3 years to stabilize the new iron balance and iron stores after changing the amount of bioavailable iron in the diet. However, 80% of the final impact is achieved in the first year. From this report, it can also be estimated that efficacy studies carried out over 5 to 6 months should reach about 40% of final impact, whereas the final impact of studies lasting less than 5 months is too difficult to interpret. Based on this information, and based on the results of published efficacy studies in women and children, the daily amount of iron necessary to achieve an improvement in iron status was estimated for each recommended iron compound. Two efficacy studies in infants are referred to but are not part of the formal analysis. These studies indicate that relatively large quantities of electrolytic iron, especially in combination with ascorbic acid, can have a positive impact on iron status [26, 27].

It is proposed that iron fortification of wheat flour should be considered at the national or regional level only if there is laboratory evidence of a high prevalence of iron deficiency and iron-deficiency anemia in women or children in the country or region concerned (iron-deficiency anemia > 5%) and that the program should aim to decrease the prevalence of iron deficiency in the target at-risk populations to levels reported in industrialized countries (< 10% iron deficiency and < 5% iron-deficiency anemia [28]). These levels should be reached in 2 to 3 years after the start of the fortification program. For simplicity, we have based our evaluation of the published efficacy studies on the potential for these values to be attained. Trials that met these criteria were considered "highly efficacious." If one or more iron status parameters or hemoglobin improved significantly without satisfying these criteria, the trial was considered to be "moderately efficacious." When the hemoglobin or iron status parameters were not significantly changed, the fortification study was considered "not efficacious." Since the duration of most of the trials was less than 12 months, the maximal reduction in the percentage of iron deficiency and the percentage of iron-deficiency anemia would not have been reached. The model developed by Hallberg et al. [25] was thus used to modify the criteria for describing the study as efficacious based on study duration. A reduction in the percentage of iron deficiency and the percentage of iron-deficiency anemia to < 12.5% and < 6%, respectively, was required for studies lasting around 9 months to be considered highly efficacious. The corresponding values for studies lasting around 5 months were < 25% and < 12.5%. A major drawback of this approach is that iron status at the start of the intervention influences the final outcome, especially for short-term studies; however, with one exception, subject selection did not affect the ability to categorize study outcome.

Efficacy studies with NaFeEDTA

NaFeEDTA has been evaluated in nine efficacy studies employing a variety of fortified foods, including wheat and maize flour as well as condiments such as fish sauce, soy sauce, curry powder, and sugar (**table 1**). Although only two of these studies were conducted with wheat flour, two were conducted with maize flour and the condiments were added to maize-based and rice-based diets, all of which are moderately high in phytate. The studies with curry powder [29], sugar [30], and soy sauce [31] and one study with fish sauce

TABLE 1. Efficacy studies with NaFeEDTA

Dose (mg/day)	Subjects and vehicle	Length of study and country	Impact	Ref
7.1	Both sexes ≥ 10 yr Curry powder	24 mo South Africa	Highly efficacious	29
4.6	Both sexes ≥ 10 yr Sugar	32 mo Guatemala	Moderately efficacious	30
8.6	Women 17–44 yr Fish sauce	6 mo Vietnam	Moderately efficacious	33
7.5	Women 16–49 yr Fish sauce	18 mo Vietnam	Highly efficacious	32
4.9	Both sexes ≥ 3 yr Soy sauce	18 mo China	Highly efficacious	31
7	Both sexes 11–18 yr Wheat flour	6 mo China	Highly efficacious	34
7	Children 3-8 yr Maize porridge	5 mo Kenya	Highly efficacious	35
3.5	Children 3–8 yr Maize porridge	5 mo Kenya	Moderately efficacious	35
1.3	Children 6–11 yr Brown bread	8 mo South Africa	No effect on iron status	36

[32] were relatively long term, lasting from 18 to 32 months. One of the fish sauce studies [33] and the studies with maize flour or wheat flour lasted only 5 to 8 months [34–36]. Eight of the nine studies reported statistically improved iron status in women and children. Five trials that provided an additional 4.9 to 7.5 mg iron/day over 5 to 24 months were judged to be highly efficacious. Three studies [30, 33, 35] providing 3.5 to 8.6 mg additional iron per day were categorized as moderately efficacious. This was due in part to unavailability of data or study design in two of them. Viteri et al. [30] did not report the percentages of iron deficiency or of iron-deficiency anemia in the study subjects. Thuy et al. [33] preselected only anemic subjects, and there was still a 20% residual prevalence of iron-deficiency anemia at the end of this 6-month trial. It is possible that the intervention would have reached the criteria for being highly efficacious if the trial had continued for a longer time. It was assumed, therefore, that the interventions of Viteri et al. [30] and Thuy et al. [33] were misclassified as moderately efficacious rather than highly efficacious because of incomplete data in the former and unsuitable study design in the latter. NaFeEDTA was only moderately efficacious in children receiving 3.5 mg additional iron per day in fortified maize meal, whereas children given brown bread that provided 1.3 mg/day as NaFeEDTA showed no improvement in iron status [36].

The recommendation for the fortification of low-extraction wheat flour with NaFeEDTA is based on the lowest dose likely to be highly efficacious (4.6 mg in the study of Viteri et al. [30]). A daily dose of 3.5 mg was considered moderately efficacious, whereas 1.3 mg had no effect on iron status in children (**table 1**). Fortification levels supplying between 3.5 mg and 4.6 mg have not been tested, so it is possible that a daily iron intake from NaFeEDTA of somewhat less than 4.6 mg may suffice. Based on mean consumption rates, the required iron concentration is 13 ppm for low-extraction wheat flour consumption levels > 300 g/day and 20 ppm for levels of 150 to 300 g/day (**table 2**). These values are lower than the 30 ppm iron recommended at Cuernavaca for the same flour consumption rates. For a lower flour consumption level of 75 to 149 g/day, the required iron concentration should be increased to 40 ppm. When the daily flour consumption is < 75 g, 92 ppm would be necessary.

These recommendations for the fortification of wheat flour with NaFeEDTA would be expected to reduce national iron-deficiency anemia and iron deficiency prevalence rates to the ranges encountered in Western countries in 2 to 3 years. They are supported by a series of well-conducted studies. Although some studies were not conducted with iron-fortified wheat or maize flours, all the fortified condiments were used within cereal-based diets relatively high in phytic acid. We concluded, therefore, that these recommendations can be stated with greater confidence than the recommendations for ferrous sulfate and ferrous fumarate that are reported in the following sections of this review. Furthermore, the enhancing properties of EDTA on iron absorption in the presence of phytate would be expected to reduce the variability in iron status responses caused by differences in overall meal bioavailability.

TABLE 2. Required flour fortification levels based on the minimum iron dose that improved iron status in efficacy studies

Iron compound	Flour consumption (g/day)	Required level (ppm)	Cuernavaca recommendation (ppm)
NaFeEDTA	> 300	13	30
	150–300	20	30
	75–149	40	30
	< 75	92	30
Ferrous sulfate	> 300	20	30
	150–300	32	30
	75–149	63	45
	< 75	142	45
Electrolytic iron	> 300	29	60
	150–300	44	60
	75–149	89	90
	< 75	200	90

Efficacy studies with ferrous sulfate

Four efficacy studies with ferrous sulfate have been reported. Two studies fed foods fortified with encapsulated sulfate (**table 3**). Wheat flour or wheat flour biscuits were fortified in three trials [21, 34, 37], and salt was fortified in the fourth [38]. The iron-fortified salt was largely added to bread prior to baking. All trials reported statistically improved iron status in schoolchildren or young women consuming an additional 7.1 to 11.8 mg iron per day over 5.5 to 9 months. The two studies that supplied 10.3 and 11.8 mg additional iron per day were categorized as highly efficacious, and the two studies providing 7.1 and 11.0 mg iron per day were categorized as moderately efficacious. It should be noted that Biebinger et al. [21] evaluated a newly developed small-particle-size (d_{50} = 40 μm) encapsulated ferrous sulfate that is suitable for flour fortification and will be retained in the flour after the sifting process.

The minimum efficacious dose for ferrous sulfate was 7.1 mg/day. It was considered to be moderately efficacious. A somewhat higher dose (~ 11 mg) was highly efficacious in two studies, but only moderately efficacious in the third (**table 3**). It is likely that the efficacy of ferrous sulfate will depend to some extent on the other food items consumed in the meal containing the fortified wheat flour. When 7.1 mg iron/day is used as

TABLE 3. Efficacy studies with ferrous sulfate

Iron compound	Dose (mg/day)	Subjects and vehicle	Length of study and country	Impact	Ref
Encapsulated ferrous sulfate[a]	11.8	Children 6–15 yr Salt (bread, fava beans)	9 mo Morocco	Highly efficacious	38
Ferrous sulfate	10.3	Women 18–40 yr Wheat flour biscuits	9 mo Thailand	Highly efficacious	37
Ferrous sulfate	11	Students 11–18 yr Wheat flour	6 mo China	Moderately efficacious	34
Encapsulated ferrous sulfate[b]	7.1	Women 18–35 yr Wheat flour biscuits	5.5 mo Kuwait	Moderately efficacious	21

a. Encapsulated with partially hydrogenated vegetable oil (Balchem, NY, USA).
b. Encapsulated with hydrogenated palm oil; mean particle size ca. 40 µm.

the required iron dose of ferrous sulfate in wheat flour, the required fortification level for countries consuming > 300 g/day is 20 ppm, lower than the 30 ppm recommended at Cuernavaca; for countries consuming 150 to 300 g flour per day, the required level is 32 ppm (**table 2**). For the countries where wheat flour consumption is between 75 and 149 g/day, the estimated required iron fortification level for ferrous sulfate is 63 ppm, and for a flour consumption of < 75 g/day, the level is 142 ppm. These latter values are much higher than those recommended at Cuernavaca. In some settings, the recommended fortification levels may be too low to achieve optimal benefit.

We were unable to discover any field trials employing ferrous fumarate that met our criteria. However, isotopic studies suggest that the absorptions of ferrous sulfate and ferrous fumarate are equivalent. Our recommendations for ferrous fumarate are therefore the same as those for ferrous sulfate.

Efficacy studies with electrolytic iron

The results of six efficacy studies in women or children conducted with electrolytic iron are shown in **table 4**. Four studies reported no improvement in iron status or presence of anemia. Three of these studies were relatively short interventions that provided only 3.2 to 7 mg additional iron per day to children over a period of 5 to 8 months. The fourth study was that of Nestel et al. [39]. These workers provided 12.5 mg extra iron per day in wheat flour over 2 years to women and children in Sri Lanka and found no change in hemoglobin. Serum ferritin was not reported. A significant improvement in iron status was reported in two studies. Zimmermann et al. [37] fed electrolytic iron-fortified biscuits to young Thai women providing 10 mg additional iron per day over 9 months. The study was judged as moderately efficacious. The prevalence of iron deficiency decreased from 45% to 21%, although there was no change in hemoglobin. Sun et al. [34] provided 21 mg additional iron per day in wheat flour to schoolchildren over 6 months. The prevalence of iron-deficiency anemia decreased from 100% to 60%.

Two additional efficacy studies have been done in infants [26, 27]. These short-term studies also indicated that relatively large amounts of electrolytic iron can have a positive effect on iron status; however, both studies included ascorbic acid, which would be

TABLE 4. Efficacy studies with electrolytic iron

Iron compound (manufacturer)	Dose (mg/day)	Subjects and vehicle	Length of study and country	Impact	Ref
A131 (Höganäs)	12.5	Women 16–50 yr Wheat flour	24 mo Sri Lanka	No change in hemoglobin	39
A131 (Höganäs)	10	Women 18–50 yr Wheat flour biscuits	9 mo Thailand	Moderately efficacious No change in hemoglobin	37
Unknown	3.2	Children 6–11 yr Brown bread	7.5 mo South Africa	No change in iron status	57
Unknown	21	Children 11–18 yr Wheat flour	6 mo China	Moderately efficacious	34
IMP	7	Children 3–8 yr Maize porridge	5 mo Kenya	No change in iron status	35
Unknown	4.5	Children 6–11 yr Brown bread	8 mo South Africa	No change in iron status	36

expected to increase iron absorption and improve the impact on iron status. Walter et al. [26] provided 12 mg extra iron per day in rice cereal for 4 months and Lartey et al. [27] provided an extra 18 mg iron per day in a complementary food based on maize, soy, and groundnuts. Both studies demonstrated that relatively large doses of electrolytic iron can have a positive impact on iron status, suggesting that this form of iron can be used if the fortification level is high enough.

The lowest dose of electrolytic iron shown to have a significant impact on iron status is 10 mg. However, it is important to note that electrolytic iron was less efficacious than ferrous sulfate in reducing iron deficiency in the trial from which this value is derived [37] and that in this study there was no reduction in the percentage of subjects with anemia. Moreover, there was a 60% residual presence of iron-deficiency anemia among children in China after a 6-month trial using more than twice this 10-mg dose [34]. Because of the uncertainty about the lowest effective dose of electrolytic iron, we have not used the information summarized in **tables 2** and **4** to formulate the recommendations for electrolytic iron. It is suggested not to change the recommendation from the Cuernavaca Workshop, which was to add electrolytic iron at twice the concentration of ferrous sulfate.

Efficacy studies with hydrogen-reduced iron

Five efficacy studies have been reported with hydrogen-reduced iron (**table 5**). Only one of these studies [37] showed an improvement in iron status. This was the SUSTAIN study in Thailand, which provided 10 mg AC-325 hydrogen-reduced iron per day in wheat flour biscuits to young Thai women over a period of 9 months. This study showed a small reduction in the number of women with iron deficiency, but no change in of the percentage of women with anemia. Another study in Zambia [40] provided 14 mg iron per day as hydrogen-reduced iron (source not specified) in maize meal to refugees over 8 months. There were no changes in iron deficiency in children, adolescents, or women, although there was a small decrease in serum transferrin receptor concentration in adolescents. The percentage of children with anemia dropped from 48% to 24%. However, the study lacked a control group, making it impossible to determine whether iron fortification played any role.

Three other studies providing 3.6 to 14.3 mg hydrogen-reduced iron per day failed to demonstrate an impact on iron status or hemoglobin. It is perhaps not surprising that providing only 3.6 mg extra iron per day (source not specified) in a seasoning powder to Thai children over 7.5 months had no impact on iron status [41]; however, providing 12.5 mg iron (source not specified) per day in wheat flour to women and children in Sri Lanka over 24 months also resulted in no change in hemoglobin [39]. The most pertinent observations are those recently reported by Biebinger et al. [21]. In this study, young Kuwaiti women were fed 14.3 mg iron per day in the form of a newly developed hydrogen-reduced iron powder (Nutrafine RS, Höganäs AB, Sweden) in wheat flour biscuits over 5.5 months. There was no improvement in their iron status. This study is important because Nutrafine RS is now marketed for food fortification in place of AC-325 hydrogen-reduced iron. The other commercial product that is used widely is Atomet™ hydrogen-reduced iron (QMP, Canada). *In vitro* solubility studies, rat hemoglobin repletion tests, and human iron tolerance studies indicate that this iron powder is likely to be the least bioavailable of all commercial iron powders [23].

There is thus no new evidence to suggest that fortification with currently available reduced iron powders will have a significant beneficial effect on iron status. It is not recommended, therefore, to use any reduced iron powder for the fortification of wheat or maize flour.

TABLE 5. Efficacy studies with reduced iron powders

Iron compound (manufacturer)	Dose (mg/day)	Subjects and vehicle	Length of study and country	Impact	Ref
Unknown	12.5	Women 14–50 yr Wheat flour	24 mo Sri Lanka	No change in hemoglobin	39
Hydrogen-reduced iron AC-325 (Höganäs)	10	Women 18–40 yr Wheat flour biscuits	9 mo Thailand	Moderate efficacy, no change in hemoglobin	37
Hydrogen-reduced iron (unknown)[a]	3.6	Children 5–13 yr Seasoning powder	7.5 mo Thailand	No change in iron status	41
Reduced (unknown)[b]	14	Both sexes 10–59 yr Maize meal	8 mo Zambia	Small decrease in iron deficiency in adolescents only, no change in other groups	40
Hydrogen-reduced iron Nutrafine RS (Höganäs)	14.3	Women 18–35 yr Wheat flour biscuits	5.5 mo Kuwait	No change in iron status	21

a. Fortificant contained multiple micronutrients.
b. Fortificant contained vitamin A.

TABLE 6. Efficacy studies with micronized ground ferric pyrophosphate (2.5 μm)

Dose (mg/day)	Subjects and vehicle	Length of study and country	Impact	Ref
18	Children 6–15 yr Salt	10 mo Morocco	Highly efficacious	43
18.6	Children 6–14 yr Salt	10 mo Morocco	Highly efficacious	44
17	Children 6–13 yr Rice	7 mo India	Moderately efficacious	46
10.5	Children 5–15 yr Salt	6 mo Côte d'Ivoire	Moderately efficacious	45

Efficacy studies with ferric pyrophosphate

The efficacy studies conducted with ground ferric pyrophosphate (2.5 μm, Dr Lohmann, Germany) are summarized in **table 6**. Although this compound has never been used for flour fortification, it is organoleptically inert and, like electrolytic iron, would appear to be about half as well absorbed as ferrous sulfate in human subjects [42]. All four efficacy studies reported a significant improvement in iron status when schoolchildren consumed between 10.5 and 18.6 mg additional iron per day over 6 to 10 months. The two studies by Zimmermann et al. [43, 44] in Morocco fed 18 and 18.6 mg iron in salt to children over 10 months. The salt was largely added to home-cooked bread, and this fortification strategy was judged as highly efficacious. A third salt study [45] providing 10.5 mg iron per day took place in Côte D'Ivoire and was judged moderately efficacious, as was a study in India where schoolchildren were provided an extra 17 mg iron per day in extruded rice added to school meals [46].

Micronized ground ferric pyrophosphate may be a suitable iron compound for wheat flour fortification at concentrations similar to those suggested for electrolytic iron. However, because it is more expensive than electrolytic iron and has not been tested in wheat or maize flour, we have not made any recommendations for its use.

Revised recommendations for iron fortification of wheat flour

Table 7 gives the new recommendations for the iron fortification of wheat flour which are based on our review and discussions at this Workshop. Before deciding on a compound, countries should first test the recommended amounts of the specific compounds in both flour and final products made from fortified flour to ensure that no unacceptable sensory changes occur. The first choices as iron fortificants for wheat flour fortification are NaFeEDTA, ferrous sulfate, and ferrous fumarate. We have the greatest confidence in the recommendations for NaFeEDTA because of the larger database and because NaFeEDTA absorption is less likely to be affected by other components of the meals in which it is eaten. The higher iron bioavailability from wheat-based foods fortified with NaFeEDTA means that lower levels of fortification iron can be added. This in turn leads to less potential for sensory changes. Moreover, NaFeEDTA has been reported not to promote lipid oxidation in stored wheat flour.

These recommendations were discussed in the plenary session at the Workshop and are consensus recommendations. Four different daily wheat flour consumption ranges were agreed upon at the Workshop (> 300, 150 to 300, 75 to 149, and < 75 g/day), and mean daily consumption levels of 350, 225, 113, and 50 g, respectively, were used to compute the suggested flour fortification levels within each of these consumption bands. Recommended values (**table 7**) were rounded to the nearest 5 ppm interval. The reason for using the mean consumption, rather than the lower limit of consumption within a designated range, is that regulations customarily stipulate a minimum requirement for fortification levels or flour nutrient content.

TABLE 7. Recommended iron fortification levels (ppm) for wheat flour according to iron compound and daily flour consumption[a]

Flour consumption (g/day)	NaFeEDTA	Ferrous sulfate or ferrous fumarate	Electrolytic iron powder
> 300	15	20	40
150–300	20	30	60
75–149	40	60	Not recommended
< 75	40	60	Not recommended

[a] These recommended levels are based on the calculated required levels presented in **table 2** but in some cases have been rounded off. For flour consumption < 75 g/day, lower levels have been recommended in order to cause no sensory changes.

It is standard procedure for producers to exceed this amount by a small margin (overage). It was therefore considered prudent to reduce the risk of excessive iron intake in individuals with high flour consumption by targeting the middle of the consumption range. The same concern applies to the risk of exceeding the acceptable daily intake (ADI) for EDTA in flour fortified with NaFeEDTA (discussed below).

It is recommended to add 15 ppm iron as NaFeEDTA for flour intakes > 300 g/day, 20 ppm iron for flour intakes of 150 to 300 g/day, and 40 ppm iron for flour intakes of 75 to 149 g/day. At these levels of iron fortification and consumption, the additional iron intake from the fortified flour would be expected to improve iron status significantly in women and children and reduce the prevalence of iron deficiency and iron-deficiency anemia to rates encountered in Western societies. A fortification level of 40 ppm is suggested for flour intakes < 75 g. At these low flour intakes, the extra iron intake from fortified flour consumption will make a useful contribution to improving iron status, but fortification of other food vehicles will be needed for an adequate iron intake to be attained. Levels of NaFeEDTA providing 15 and 20 ppm iron are considered unlikely to cause adverse sensory changes. Such changes are more likely with 40 ppm iron as NaFeEDTA. If they occur, encapsulated NaFeEDTA should be considered.

NaFeEDTA is the only iron compound that is recommended for the fortification of high-extraction (> 0.8% ash) wheat flour. The recommended fortification levels are the same as for low-extraction (≤ 0.8% ash) wheat flour: 15 ppm for flour consumption > 300 g/day, 20 ppm for 150 to 300 g/day, and 40 ppm for < 150 g/day. The higher phytate content in high-extraction wheat flour is expected to reduce the percent iron absorption, but it is anticipated that this will be offset by an enhancement in absorption of the native flour iron by the EDTA. NaFeEDTA is also recommended for wheat products, such as pasta, in which there is no fermentation process during manufacture. There are no published human efficacy studies to support the recommendations for the fortification of high-extraction flour or pasta.

The widespread use of NaFeEDTA will depend on clarification of the putative, but as yet unsubstantiated, potential risks of increasing the EDTA consumption of the whole population. The following recommendation [47] for the use of NaFeEDTA as a food additive was made at the 68th Meeting of the Joint FAO/WHO Expert Committee on Food Additives:

> Sodium iron EDTA is suitable as a source of iron for food fortification to fulfil nutritional iron requirements, provided that the total intake of iron from all food sources including contaminants does not exceed the Provisional Maximum Tolerable Daily Intake of 0.8 mg/kg body weight. Total intake of EDTA should not exceed acceptable levels, also taking into account the intake of EDTA from the food additive use of other EDTA compounds. An ADI of 0–2.5 mg/kg body weight was previously established for calcium disodium and disodium salts of EDTA, equivalent to up to 1.9 mg/kg body weight EDTA [47].

This specification was noted without revision at the 31st Session of the Joint FAO/WHO Food Standards Programme Codex Alimentarius Commission in Geneva, 30 June to 4 July 2008 [48].

The fortification levels proposed in this document would deliver approximately 4.5 mg/day of additional iron in the form of NaFeEDTA and 23 mg EDTA. This would amount to 0.42 mg EDTA/kg for a 55-kg woman, well below the ADI. However, EDTA consumption from mass fortification with NaFeEDTA may approach or exceed the ADI for relatively short periods of time in very young children when growth is rapid and caloric intake is high in relation to body weight. A 1-year-old child would be expected to weigh approximately 10 kg and have a caloric intake approximately half that of an adult woman. Under these circumstances, mean EDTA intake may exceed the ADI for EDTA of 1.9 mg/kg if wheat flour accounts for the same proportion of caloric intake in the child as in the adult. It will also be important for countries to evaluate EDTA intake from other sources, although this is likely to be low. These factors should be considered by countries planning to implement NaFeEDTA fortification of wheat flour or other food products. As indicated above, the desirable impact on iron status may be achievable with modestly lower levels of NaFeEDTA.

Ferrous sulfate has also consistently shown good efficacy in a variety of iron-fortified foods. It is widely used to fortify infant formulas and is the iron compound chosen by WHO for food fortification. It has been used in the highly successful wheat flour fortification program in Chile, where it provides about 6 mg additional iron per day in about 200 g wheat flour [2]. This amount is similar to the 7.1 mg/day minimum amount reported to be efficacious in the studies reviewed in this article. Ferrous fumarate is considered to be as efficacious as ferrous sulfate on the basis of isotopic experiments in human volunteers [49, 50]. However, there are no efficacy studies to support this assumption. Ferrous sulfate is preferred to ferrous fumarate but is more likely to lead to unacceptable sensory changes in some situations. Encapsulation of either compound will prevent lipid oxidation in stored flours, with no impact on bioavailability [51]. The recommended levels of fortification when using these compounds are 20 ppm iron for flour consumption > 300 g/day and 30 ppm iron for flour consumption between 150 and 300 g/day. For flour consumption < 150 g/day, sensory changes may result with the recommended level of 60 ppm unless the iron compounds are encapsulated. Ferrous sulfate and ferrous fumarate are not recommended for the fortification of high-extraction (high-phytate) flours.

Electrolytic iron is the second-choice iron compound for wheat flour fortification. It should be considered when the first-choice compounds (NaFeEDTA, ferrous sulfate, and ferrous fumarate) cause sensory changes or are considered too expensive. Although one efficacy study suggested that 10 mg iron/day as electrolytic would be adequate, the results from other studies were not consistent. It is recommended, therefore, that the amount of electrolytic iron needed per day should be double the iron level recommended for ferrous sulfate, i.e., 14.2 mg/day. It would be helpful to have additional efficacy trials to confirm that this level of addition is adequate.

Another potential disadvantage of poorly soluble compounds such as electrolytic iron is that iron-deficient subjects up-regulate absorption from these compounds less efficiently than absorption from ferrous sulfate [52]. The advantages of electrolytic iron are that it causes few if any sensory changes and is less expensive. The recommended level of fortification for electrolytic iron is 40 ppm iron for flour consumption > 300 g/day and 60 ppm iron for flour consumption of 150 to 300 g/day. Electrolytic iron is not recommended when flour consumption is < 150 g/day because the high fortification levels required may cause sensory changes. Electrolytic iron also is not recommended for fortification of high-phytate flours.

There is no evidence to support the use of hydrogen-reduced iron powders or atomized reduced iron powders for wheat or maize flour fortification. These compounds are less well absorbed than electrolytic iron and are not recommended for wheat flour fortification. Although the newly developed Nutrafine RS hydrogen-reduced iron was not found to be efficacious, manufacturers are encouraged to continue the development of low-cost hydrogen-reduced iron powders. However, the efficacy of any new product should be tested in human volunteers and demonstrated to be equivalent to or better than that of electrolytic iron.

Recommendations for the iron fortification of maize flour

A detailed evaluation of maize flour fortification was not attempted in this review. There is much less experience with fortifying maize flours with iron than with fortifying wheat flours; however, similar considerations apply. Previous recommendations [53] can still be used. More research is needed to evaluate the best approach for maize flour fortification, especially the fortification of nixtamalized maize flour.

Predicted impact of current national programs of iron-fortified wheat flour

The marked reduction in the prevalence of iron deficiency among young children in the United States is attributed to the fortification of infant formulas and weaning foods with iron [54]. Similarly, the low prevalence of iron-deficiency anemia in female adolescents and women of childbearing age is attributed in part to the consumption of iron-fortified wheat flour [50]. Reports from Denmark and Sweden also provide indirect evidence of the impact of fortification. The withdrawal of mandatory iron fortification of wheat flour with carbonyl iron in Denmark in 1987 led to a decrease in serum ferritin levels among blood donors, a group that would be expected to have high iron requirements [13]. Mandatory fortification of wheat flour with carbonyl iron in Sweden was discontinued in 1994. Six years later, a 20% increase in the prevalence of iron deficiency was observed among 15- and 16-year-old girls [14]. Finally, the low prevalence of iron deficiency among women of childbearing age in Chile is attributed to the fortification of wheat flour with ferrous sulfate. The fortification level is 30 ppm, with an average daily intake of about 200 g per capita delivering an additional 6 mg iron [55].

Details of the current mandatory, voluntary, World Food Programme, and planned national and regional wheat flour fortification programs are summarized in **table 8**. The type of program, the iron compound used, and the level of iron added were taken from the Cereal Fortification Handbook compiled by the Micronutrient Initiative [19]. The wheat flour consumption data were based on Food and Agriculture Organization (FAO) wheat consumption data [56]. Most of the current wheat flour fortification programs would be expected to have little impact on iron status at the national level. The main reason is the failure to specify a recommended iron compound. Of the 78 programs listed in **table 8**, 47 do not stipulate a specific iron compound. These programs are understood to be using atomized or hydrogen-reduced iron powders because of their low cost and good sensory properties. Reduced iron is specified in Bangladesh, Fiji, and Qatar and permitted in the Philippines. A recommended iron compound (ferrous sulfate, ferrous fumarate, electrolytic iron, or NaFeEDTA) is specified in the remaining 27 countries. However, the average per capita wheat flour consumption for the whole country is < 75 g/person/day in 13 countries and 76 and 88 g/person/day in Costa Rica and the Dominican Republic, respectively. These consumption rates are too low for fortification of wheat flour alone to have an impact on iron deficiency based on national statistics, although it is important to note that average flour consumption may not reflect major

TABLE 8. National iron fortification programs with wheat flour

Country or region	Type of program	Flour consumption (g/day)	Iron compound	Iron fortification level (ppm)
Afghanistan	WFP	208	NS	37.5
Argentina	Mandatory	229	Sulfate	30
Azerbaijan	Voluntary	404	NS	40
Bahrain	Mandatory	200	NS	60
Bangladesh	WFP	49	Reduced	37.5
Barbados	Regional	111	NS	44
Belize	Regional	149	NS	60
Bolivia	Mandatory	63	Fumarate	35
Brazil	Mandatory	90	NS	42
Canada	Mandatory	159	NS	44
Caribbean	Regional	150	NS	29
Central African Republic	Planned	12	NS	45
Chile	Mandatory	215	Sulfate	30
China	Voluntary	115	FeEDTA	24
Colombia	Mandatory	50	NS	44
Congo DRC	WFP	11	Sulfate	45
Costa Rica	Mandatory	88	Fumarate	55
Côte d'Ivoire	Mandatory	29	Electrolytic	60
Cuba	Mandatory	76	Sulfate	45
Cyprus	Voluntary	193	NS	45
Dominican Republic	Voluntary	58	Fumarate	55
Ecuador	Mandatory	60	NS	55
Egypt	Planned	256	Sulfate	30
El Salvador	Mandatory	58	Fumarate	55
Fiji	Regional	233	Reduced	60
Georgia	Planned	179	NS	50
Ghana	Planned	39	Fumarate	45
Guatemala	Mandatory	60	Fumarate	55
Guinea	Mandatory	25	NS	54
Guyana	Voluntary	120	NS	29
Haiti	Regional	61	NS	44
Honduras	Mandatory	58	Fumarate	55
Indonesia	Mandatory	33	Electrolytic	50
Iran	Mandatory	354	Sulfate	30
Iraq	Voluntary	223	NS	30
Israel	Planned	221	NS	37.5
Jamaica	Voluntary	238	NS	44
Jordan	Mandatory	186	Sulfate	34
Kazakhstan	Voluntary	278	NS	40
Kuwait	Mandatory	209	NS	60
Kyrgyz Republic	Voluntary	380	NS	40

continued

TABLE 8. National iron fortification programs with wheat flour *(continued)*

Country or region	Type of program	Flour consumption (g/day)	Iron compound	Iron fortification level (ppm)
Lebanon	Regional	204	Sulfate	30
Lesotho	Voluntary	75	NS	35
Malawi	Planned	6	NS	30
Malaysia	Voluntary	102	NS	44
Mexico	Mandatory	60	Sulfate	40
Mongolia	Voluntary	202	NS	40
Morocco	Planned	366	NS	45
Nicaragua	Mandatory	55	Fumarate	55
Nigeria	Mandatory	36	NS	40.7
Oman	Mandatory	160	NS	30
Pakistan	Planned	248	FeEDTA	10
Palestine	Mandatory	213	Sulfate	25
Panama	Mandatory	74	NS	60
Paraguay	Mandatory	22	Sulfate	45
Peru	Mandatory	102	NS	28
Philippines	Mandatory	44	Sulfate, fumarate, reduced	70/Reduced, 50/sulfate, fumarate
Qatar	Mandatory	160	Reduced	60
Russia	Planned	267	NS	30
Saudi Arabia	Mandatory	206	NS	36.3
Sierra Leone	Voluntary	23	NS	30
South Africa	Mandatory	96	NS	35
St. Vincent	Voluntary	113	NS	44
Switzerland	Voluntary	158	NS	29
Syria	Mandatory	200	Sulfate	30
Tajikistan	Voluntary	302	NS	40
Trinidad and Tobago	Mandatory	166	NS	30
Turkmenistan	Mandatory	450	Sulfate	20
UAE	Mandatory	206	NS	30
Uganda	Planned	7	Fumarate	40
United Kingdom	Mandatory	191	NS	16.5
United States	Regional	182	NS	44
Uruguay	Mandatory	211	Sulfate	30
Uzbekistan	Regional	284	NS	40
Venezuela	Mandatory	85	NS	16
Vietnam	Planned	18	NS	60
Yemen	Mandatory	185	NS	30
Zambia	Voluntary	33	NS	28.9

FeEDTA, iron ethylenediaminetetraacetate; NS, iron compound not specified; WFP, World Food Programme
Source: Ranum and Wesley [19], FAO/WHO [56].

variations in consumption rates in different regions within a single country. If this is the case, fortification in the regions with higher consumption rates could have a significant impact. Specifications for levels of addition should be based on consumption rates in regions with intakes high enough to permit fortification to be effective.

In Bolivia, Costa Rica, the Dominican Republic, El Salvador, Guatemala, Honduras, and Nicaragua, wheat flour consumption is only 55 to 88 g/day, but it is fortified with 35 to 60 ppm iron as ferrous fumarate, providing some 2 to 4 mg extra iron per day. This amount of iron by itself would be judged as too low to have a positive impact on iron status, but it would make a useful positive contribution if combined with the fortification of other food vehicles such as maize.

NaFeEDTA is specified for voluntary programs in China and a planned program in Pakistan. Although an impact on iron status at the regional level might be anticipated in China, it might not be evident in a national database, because wheat is not a major staple in some parts of China. The addition level in Pakistan is lower than that recommended and may therefore be too low to allow confidence of a significant impact. Ferrous sulfate is specified in Palestine, but the addition level is inadequate (25 ppm).

The nine countries that can expect a positive impact from wheat flour fortification programs use ferrous sulfate. They are Argentina, Chile, Egypt, Iran, Jordan, Lebanon, Syria, Turkmenistan, and Uruguay. They could provide an average of 5.4 to 9.6 mg additional iron per day via fortified flour with optimal coverage.

The way forward

Despite a strong interest by flour millers and national governments in the use of wheat flour fortification to combat iron deficiency and iron-deficiency anemia, it would appear that only 9 of the 78 national wheat flour programs could expect to have the desired nutritional impact. Most millers do not follow the Cuernavaca (2004) [20] or WHO (2006) [2] guidelines for wheat flour fortification. In many countries, wheat flour is still fortified with atomized and hydrogen-reduced elemental iron powders. These iron powders are not recommended for food fortification because of poor absorption, but they are commonly used because they cost less and cause few if any sensory changes. Other national wheat flour fortification programs appear to use fortification levels that are too low in relation to the wheat flour consumption patterns, or have too little coverage. It seems unlikely, therefore, that a meaningful reduction in the worldwide prevalence of iron deficiency will be achieved via wheat flour fortification unless current practices are changed. The first step is to modify national regulations for wheat flour fortification so that only recommended iron compounds are added at concentrations necessary to achieve a satisfactory impact. There is an also an urgent need for further efforts to resolve the regulatory issues that have limited the use of NaFeEDTA. Once the millers have clear guidelines for the efficacious fortification of wheat flour with iron, the small extra cost will be a price worth paying for the meaningful health benefit to women and children.

References

1. McLean E, Egli I, de Benoist B, Wojdyla D. Worldwide prevalence of anemia in preschool aged children, pregnant women and non-pregnant women of reproductive age. In: Kraemer K, Zimmermann MB, eds. Nutritional anemia. Basel, Switzerland: Sight and Life Press, 2007:1–12.
2. World Health Organization/Food and Agriculture Organization. Guidelines on food fortification with micronutrients. Geneva: WHO, 2006.
3. Lynch SR, Skikne BS, Cook JD. Food iron absorption in idiopathic hemochromatosis. Blood 1989;74:2187–93.
4. Hurrell R. How to ensure adequate iron absorption from iron-fortified food. Nutr Rev 2002;60:S7–15; discussion S43.
5. Zimmermann MB, Chaouki N, Hurrell RF. Iron deficiency due to consumption of a habitual diet low in bioavailable iron: a longitudinal cohort study in Moroccan children. Am J Clin Nutr 2005;81:115–21.
6. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet 2006;367:1066–74.
7. Scholl TO, Hediger ML, Fischer RL, Shearer JW. Anemia vs iron deficiency: increased risk of preterm delivery in a prospective study. Am J Clin Nutr 1992;55:985–8.
8. Preziosi P, Prual A, Galan P, Daouda H, Boureima H, Hercberg S. Effect of iron supplementation on the iron status of pregnant women: consequences for newborns. Am J Clin Nutr 1997;66:1178–82.
9. Lozoff B. Iron deficiency and child development. Food Nutr Bull 2007;28:S560–71.
10. Horten S, Ross J. Corrigendum to "The economics of iron deficiency" (Food Policy 28 (2003) 51–75). Food Policy 2003;32:141–3.
11. de Silva A, Atukorala S, Weerasinghe I, Ahluwalia N. Iron supplementation improves iron status and reduces morbidity in children with or without upper respiratory tract infections: a randomized controlled study in Colombo, Sri Lanka. Am J Clin Nutr 2003;77:234–41.
12. Sazawal S, Black RE, Ramsan M, Chwaya HM, Stoltzfus RJ, Dutta A, Dhingra U, Kabole I, Deb S, Othman MK, Kabole FM. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised,

placebo-controlled trial. Lancet 2006;367:133–43.
13. Milman N, Byg KE, Ovesen L, Kirchhoff M, Jurgensen KS. Iron status in Danish men 1984–94: a cohort comparison of changes in iron stores and the prevalence of iron deficiency and iron overload. Eur J Haematol 2002;68:332–40.
14. Hallberg L, Hulthen L. Perspectives on iron absorption. Blood Cells Mol Dis 2002;29:562–73.
15. Nemeth E, Ganz T. Regulation of iron metabolism by hepcidin. Annu Rev Nutr 2006;26:323–42.
16. Bothwell T, Charlton R, Cook JD, Finch C. Iron metabolism in man. London: Blackwell Scientific Publications, 1979.
17. Gable CB. Hemochromatosis and dietary iron supplementation: implications from US mortality, morbidity, and health survey data. J Am Diet Assoc 1992;92:208–12.
18. Pippard M. Secondary iron overload. In: Brock JH, Halliday JW, Pippard MJ, Powell LW, eds. Iron metabolism in health and disease. London: WB Saunders, 1994.
19. Ranum P, Wesley A. Cereal fortification handbook. Ottawa Micronutrient Initiative, 2008.
20. Flour Fortification Initiative. Report of the Workshop on Wheat Flour Fortification, Cuernavaca, Mexico, 1–3 December 2004. Available at: http://www.sph.emory.edu/wheatflour/CKPAFF/index.htm. Accessed 20 November 2009.
21. Biebinger R, Zimmermann M, Al-Hooti S, Al-Hamed N, Al-Salem E, Zafar T, Kabir Y, Al-Obaid I, Petry N, Hurrell R. Efficacy of wheat-based biscuits fortified with microcapsules containing ferrous sulfate and potassium iodate or a new hydrogen-reduced elemental iron: a randomized, double-blind, controlled trial in Kuwaiti women. Br J Nutr 2009;102:1362-9.
22. Hurrell R, Bothwell T, Cook JD, Dary O, Davidsson L, Fairweather-Tait S, Hallberg L, Lynch S, Rosado J, Walter T, Whittaker P. The usefulness of elemental iron for cereal flour fortification: a SUSTAIN Task Force report. Sharing United States Technology to Aid in the Improvement of Nutrition. Nutr Rev 2002;60:391–406.
23. Lynch SR, Bothwell T. A comparison of physical properties, screening procedures and a human efficacy trial for predicting the bioavailability of commercial elemental iron powders used for food fortification. Int J Vitam Nutr Res 2007;77:107–24.
24. Bothwell TH, MacPhail AP. The potential role of NaFeEDTA as an iron fortificant. Int J Vitam Nutr Res 2004;74:421–34.
25. Hallberg L, Hulthen L, Garby L. Iron stores in man in relation to diet and iron requirements. Eur J Clin Nutr 1998;52:623–31.
26. Walter T, Dallman PR, Pizarro F, Velozo L, Pena G, Bartholmey SJ, Hertrampf E, Olivares M, Letelier A, Arredondo M. Effectiveness of iron-fortified infant cereal in prevention of iron deficiency anemia. Pediatrics 1993;91:976–82.
27. Lartey A, Manu A, Brown KH, Peerson JM, Dewey KG. A randomized, community-based trial of the effects of improved, centrally processed complementary foods on growth and micronutrient status of Ghanaian infants from 6 to 12 mo of age. Am J Clin Nutr 1999;70:391–404.
28. Centers for Disease Control and Prevention. Iron deficiency—United States, 1999–2000. MMWR Morb Mortal Wkly Rep 2002;51:897–9.
29. Ballot DE, MacPhail AP, Bothwell TH, Gillooly M, Mayet FG. Fortification of curry powder with NaFe(III)EDTA in an iron-deficient population: report of a controlled iron-fortification trial. Am J Clin Nutr 1989;49:162–9.
30. Viteri FE, Alvarez E, Batres R, Torun B, Pineda O, Mejia LA, Sylvi J. Fortification of sugar with iron sodium ethylenediaminotetraacetate (FeNaEDTA) improves iron status in semirural Guatemalan populations. Am J Clin Nutr 1995;61:1153–63.
31. Chen J, Zhao X, Zhang X, Yin S, Piao J, Huo J, Yu B, Qu N, Lu Q, Wang S, Chen C. Studies on the effectiveness of NaFeEDTA-fortified soy sauce in controlling iron deficiency: a population-based intervention trial. Food Nutr Bull 2005;26:177–86; discussion 87–9.
32. Van Thuy P, Berger J, Nakanishi Y, Khan NC, Lynch S, Dixon P. The use of NaFeEDTA-fortified fish sauce is an effective tool for controlling iron deficiency in women of childbearing age in rural Vietnam. J Nutr 2005;135:2596–601.
33. Thuy PV, Berger J, Davidsson L, Khan NC, Lam NT, Cook JD, Hurrell RF, Khoi HH. Regular consumption of NaFeEDTA-fortified fish sauce improves iron status and reduces the prevalence of anemia in anemic Vietnamese women. Am J Clin Nutr 2003;78:284–90.
34. Sun J, Huang J, Li W, Wang L, Wang A, Huo J, Chen J, Chen C. Effects of wheat flour fortified with different iron fortificants on iron status and anemia prevalence in iron deficient anemic students in Northern China. Asia Pac J Clin Nutr 2007;16:116–21.
35. Andang'o PE, Osendarp SJ, Ayah R, West CE, Mwaniki DL, De Wolf CA, Kraaijenhagen R, Kok FJ, Verhoef H. Efficacy of iron-fortified whole maize flour on iron status of schoolchildren in Kenya: a randomised controlled trial. Lancet 2007;369:1799–806.
36. van Stuijvenberg ME, Smuts CM, Lombard CJ, Dhansay MA. Fortifying brown bread with sodium iron EDTA, ferrous fumarate, or electrolytic iron does not affect iron status in South African schoolchildren. J Nutr 2008;138:782–6.
37. Zimmermann MB, Winichagoon P, Gowachirapant S, Hess SY, Harrington M, Chavasit V, Lynch SR, Hurrell RF. Comparison of the efficacy of wheat-based snacks fortified with ferrous sulfate, electrolytic iron, or hydrogen-reduced elemental iron: randomized, double-blind, controlled trial in Thai women. Am J Clin Nutr 2005;82:1276–82.
38. Zimmermann MB, Zeder C, Chaouki N, Saad A, Torresani T, Hurrell RF. Dual fortification of salt with iodine and microencapsulated iron: a randomized, double-blind, controlled trial in Moroccan schoolchildren. Am J Clin Nutr 2003;77:425–32.
39. Nestel P, Nalubola R, Sivakaneshan R, Wickramasinghe AR, Atukorala S, Wickramanayake T, Team FFT. The use of iron-fortified wheat flour to reduce anemia among the estate population in Sri Lanka. Int J Vitam Nutr Res 2004;74:35–51.
40. Seal A, Kafwembe E, Kassim IA, Hong M, Wesley A, Wood J, Abdalla F, van den Briel T. Maize meal fortification is associated with improved vitamin A and iron status in adolescents and reduced childhood anaemia in a food aid-dependent refugee population. Public Health Nutr 2008;11:720–8.
41. Winichagoon P, McKenzie JE, Chavasit V, Pongcharoen

T, Gowachirapant S, Boonpraderm A, Manger MS, Bailey KB, Wasantwisut E, Gibson RS. A multimicronutrient-fortified seasoning powder enhances the hemoglobin, zinc, and iodine status of primary school children in North East Thailand: a randomized controlled trial of efficacy. J Nutr 2006;136:1617–23.

42. Fidler MC, Walczyk T, Davidsson L, Zeder C, Sakaguchi N, Juneja LR, Hurrell RF. A micronised, dispersible ferric pyrophosphate with high relative bioavailability in man. Br J Nutr 2004;91:107–12.
43. Zimmermann MB, Wegmueller R, Zeder C, Chaouki N, Rohner F, Saissi M, Torresani T, Hurrell RF. Dual fortification of salt with iodine and micronized ferric pyrophosphate: a randomized, double-blind, controlled trial. Am J Clin Nutr 2004;80:952–9.
44. Zimmermann MB, Wegmueller R, Zeder C, Chaouki N, Biebinger R, Hurrell RF, Windhab E. Triple fortification of salt with microcapsules of iodine, iron, and vitamin A. Am J Clin Nutr 2004;80:1283–90.
45. Wegmuller R, Camara F, Zimmermann MB, Adou P, Hurrell RF. Salt dual-fortified with iodine and micronized ground ferric pyrophosphate affects iron status but not hemoglobin in children in Côte d'Ivoire. J Nutr 2006;136:1814–20.
46. Moretti D, Zimmermann MB, Muthayya S, Thankachan P, Lee TC, Kurpad AV, Hurrell RF. Extruded rice fortified with micronized ground ferric pyrophosphate reduces iron deficiency in Indian schoolchildren: a double-blind randomized controlled trial. Am J Clin Nutr 2006;84:822–9.
47. World Health Organization/Food and Agriculture Organization. Joint FAO/WHO Expert Committee on Food Additives, Sixty-eighth meeting, Geneva, 19–28 June 2007. Available at: http://www.fao.org/ag/agn/agns/files/jecfa68_final.pdf. Accessed 20 November 2009.
48. World Health Organization/Food and Agriculture Organization. Joint FAO/WHO Food Standards Programme Codex Alimentarius Commission, 31st Session, Geneva, 30 June–4 July, 2008.
49. Hurrell RF, Reddy MB, Dassenko SA, Cook JD. Ferrous fumarate fortification of a chocolate drink powder. Br J Nutr 1991;65:271–83.
50. Hurrell R. Iron. In: Hurrell R, ed. The mineral fortification of foods, 1st ed. Surrey, UK: Leatherhead Food RA, 1999:54–93.
51. Zimmermann MB. The potential of encapsulated iron compounds in food fortification: a review. Int J Vitam Nutr Res 2004;74:453–61.
52. Moretti D, Zimmermann MB, Wegmuller R, Walczyk T, Zeder C, Hurrell RF. Iron status and food matrix strongly affect the relative bioavailability of ferric pyrophosphate in humans. Am J Clin Nutr 2006;83:632–8.
53. Dary O. Lessons learned with iron fortification in Central America. Nutr Rev 2002;60:S30–3.
54. Fomon S. Infant feeding in the 20th century: formula and beikost. J Nutr 2001;131:409S–20S.
55. Hertrampf E. Iron fortification in the Americas. Nutr Rev 2002;60:S22–5.
56. Food and Agriculture Organization/World Health Organization, FAOSTAT, Food Supply, Crops Primary Equivalent. Available at: http://faostat.fao.org/site/609/default.aspx#ancor. Accessed 8 February 2009.
57. van Stuijvenberg ME, Smuts CM, Wolmarans P, Lombard CJ, Dhansay MA. The efficacy of ferrous bisglycinate and electrolytic iron as fortificants in bread in iron-deficient school children. Br J Nutr 2006;95:532–8.