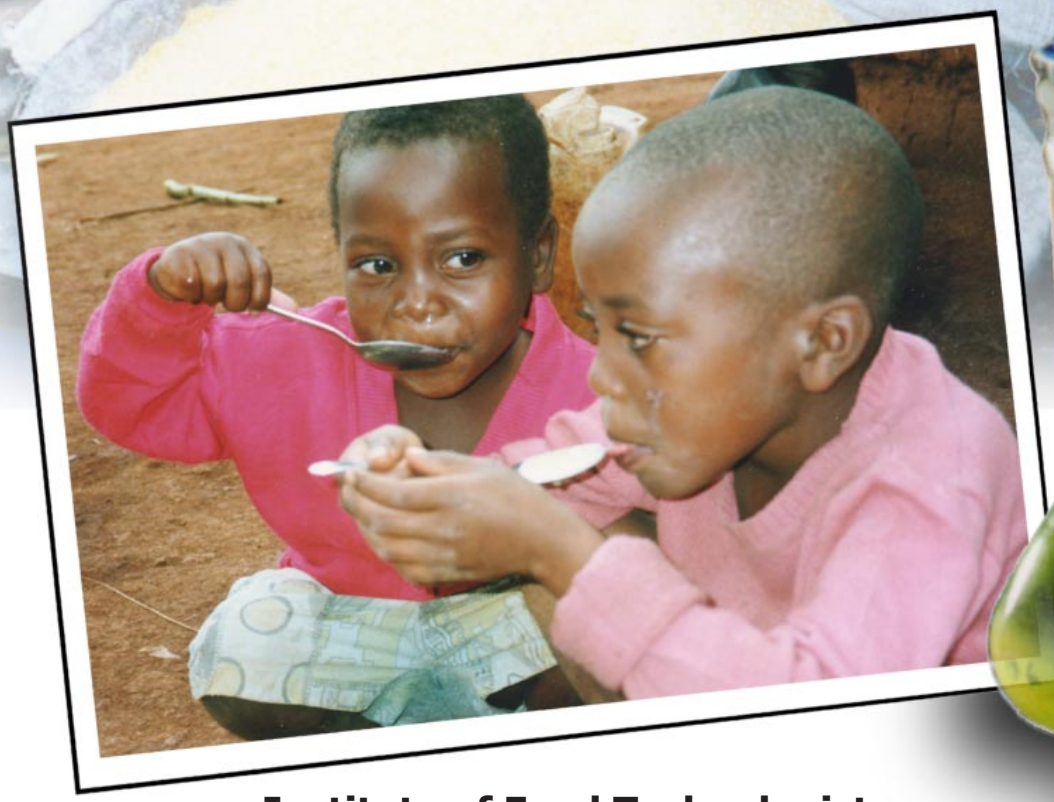
SUSTAIN

SHARING UNITED STATES TECHNOLOGY TO AID IN THE IMPROVEMENT OF NUTRITION

Forum on Iron Fortification

Forum Proceedings



Institute of Food Technologists
Annual Meeting
June 21, 1998
Atlanta, Georgia

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MISSION

The mission of SUSTAIN is to share science and technology to improve nutrition in developing countries. We do this by engaging industry, the scientific research community and governments in collaborative efforts to enhance the nutritive quality of food staples and by encouraging technologic innovation.

ORIGINS

SUSTAIN originated as a volunteer-based initiative to share food technology expertise with developing countries. SUSTAIN's early programs supported developing country food industries striving to improve product quality, food safety, packaging and marketing. SUSTAIN volunteers, drawn largely from U.S. food industries, provided requesting food companies with hands-on expertise to achieve these goals.

In the mid 1990's, SUSTAIN began to devote significant program attention to addressing the nutritional challenges of vulnerable populations. Our appreciation of the critical role micronutrients play in health and survival, particularly for infants, children, and women of childbearing age, led us to target applications of food science and technology to the pervasive problem of micronutrient deficiencies in developing countries.

BUILDING PARTNERSHIPS TO IMPROVE NUTRITION

In 1999, SUSTAIN launched operations as a 501(c)(3) non-profit organization whose goal remains technology sharing to improve global nutrition. SUSTAIN works as a catalyst organization, building partnerships across industry, the scientific and public health communities and government to improve the quality of food, and thus the quality of life for people in developing countries. SUSTAIN also sponsors research and encourages industry's development of innovative technologies in support of nutritional enhancements.

WWW.SUSTAINTECH.ORG

ACKNOWLEDGEMENTS

SUSTAIN wishes to thank the Institute of Food Technologists (IFT) for their support and cooperation in holding the *IFT Forum on Iron Fortification.* Held in Atlanta, Georgia on June 21, 1998, SUSTAIN sponsored the forum in conjunction with the IFT Annual Meeting. SUSTAIN also would like to thank moderators Samuel Kahn of USAID, Peter Ranum of SUSTAIN and the speakers at the forum for their valuable contributions to this activity.

This report was compiled and edited by SUSTAIN consultant, Jack Bagriansky. The activity was coordinated by Teresa M. Lozeau, SUSTAIN Program Manager and Erica Stewart, SUSTAIN Program Associate. SUSTAIN consultant, David Russo, designed the cover and published the document.

TABLE OF CONTENTS

Preface

Samuel Kahn
USAID

Iron deficiency anemia (IDA) is the most prevalent nutritional deficiency worldwide, and according to WHO, impacts nearly one-third of the earth's population. It is a leading cause of death among a one-half million women who die in childbirth every year. Among children, it is associated with reduced immune response, increased infection, and retarded physical growth and mental development. IDA is particularly devastating in the developing world where 1.3 billion people are affected. In many nations in South and East Asia, Sub-Saharan Africa and Latin America, up to 80% of women and children suffer the physical, mental and socio-economic burden of iron deficiency. While there are a variety of causes, the most common cause of IDA is dietary.

Iron is key for the synthesis of hemoglobin. Hemoglobin is essential in the delivery of oxygen from the lungs to body organs and tissues. When sufficient iron is not available to the body, the consequences are profound. Without sufficient iron for optimum transport of oxygen to the muscles and brain, a debilitating fatigue and lethargy sets in, sapping strength and energy and lowering work capacity and productivity.

These consequences affect more than half of the population of many developing countries, dampening prospects for economic development. A recent review calculated economic losses due to iron deficiency. Reduced cognitive development in children and lower work performance in adults were conservatively calculated at $4 per capita or almost 1% of GDP. Losses in South Asia alone were estimated at close to $5 billion annually.

Against this backdrop, the fortification of food staples and condiments with iron salts offers an opportunity to improve many lives throughout the world. Iron fortification is one of the least expensive and potentially most effective strategies to supply micronutrients to at-risk populations. The food science is well known, the investment modest, and the returns immeasurable. However, adapting technologies used in the industrial world to the food processing, dietary and cooking patterns of developing countries presents a number of challenges.

The goal of iron fortification is to provide vulnerable populations with iron in a bioavailable form that meets their bodies' needs and benefits their growth, development and productivity. This involves more than simply adding iron to food. Iron absorption, the ultimate measure of the biological value of added iron, is a complex interplay of the fortificant, food vehicle, and other foods consumed in a meal. In countries in Asia, Africa and Latin America, staple diets of corn, beans, wheat and rice

contain compounds that inhibit iron absorption. Tea and coffee, beverages taken with meals in much of the world, contain tannins that greatly reduce absorption. Unfortunately, the more absorbable iron salts with a higher biological value are also more chemically reactive and can adversely effect food quality.

While many countries are currently implementing or initiating fortification programs, these issues have slowed the progress of fortification programs. Yet new techniques, new compounds, and new success stories are emerging. This forum will present the current state of our understanding of iron fortification as a means to reduce iron deficiency anemia in developing countries and an opportunity discuss encouraging scientific advancements. The progress is heartening, the potential enormous.

Iron Fortification: Prevention of Iron Deficiency Anemia For Developing Countries

Ray Yip
UNICEF

Prevalence of Iron Deficiency

Iron deficiency is the most prevalent nutritional disorder in the developing world and the only remaining micronutrient deficiency still of public health importance in developed countries. Using anemia as an indicator, almost half of all infants and pregnant women in developing countries suffer from iron deficiency. About 20-25% of non-pregnant women are also iron deficient.

It is worth noting that anemia represents the more severe end of the spectrum of iron deficiency. In its milder form, individuals have depleted iron stores yet are not considered anemic as they have adequate iron for normal physiological function. In general, for every case of iron deficiency anemia detected in a given population, there is another one or two cases of the milder form of iron deficiency. In other words, using anemia to estimate the burden of iron deficiency underestimates the actual problem of iron deficiency.

Differential Iron Requirements Determine High Risk Groups

Women and children are clearly more vulnerable to iron deficiency anemia. This is because different groups have different daily iron requirements. These requirements vary among different population groups and stages of the life cycle. For example, men need 1 mg of iron per day while an average woman who is smaller in size needs 50% more iron, or 1.5 mg a day. This higher requirement for women is mainly because of menstrual blood loss. Pregnant women require 4.5 mg day. This is more than four times the iron required by an adult man and three times the requirement for non-pregnant women.

A reasonably good diet only provides 1.5-2 mg of absorbable iron per day, about half of this requirement. Based on this gap of intake and requirement, routine supplementation is suggested for pregnant women. However, in most developing countries, because of poor dietary quality or low intake of food from animal sources (a better source of iron), many women can not meet their iron requirement even when not pregnant. Under these circumstances, efforts to improve baseline iron status are needed. Fortification appears to be the most effective strategy to do so.

Table 1

Segment	Absorbed Iron Requirement (in mg per day)	Dietary Iron Needed at 8% Absorption to Satisfy Absorbed Iron Requirement
Adult Men	*1*	*12.5*
Adult Women	*1.5*	*18.75*
Pregnant Women	*4.5*	*56.25*
Infants	*0.8*	*10*

Infants require only .8 mg of absorbed iron a day—less than men do. However, children consume far less then men, and often the quality of the iron is inferior. Assuming an iron absorption rate of 8%, 1800 kcal of iron with average bioavailability must be consumed by young children to meet the requirement. However, the average infant diet in the developing world is only 800 calories and contains less iron than the typical adult diet. Generally, the infant diet in developing countries provides only one-half the absorbed iron requirement. For this reason, without a special provision to assure greater iron content of infant diet, most will develop some degree of iron deficiency.

Determinants of Iron Deficiency

Iron deficiency is caused by an intake of iron that does not meet the iron requirement and/or by blood loss. Inadequate intake is caused by a variety of factors. A diet may lack sufficient iron content (quantity) or bioavailability (quality). From a nutritional point of view, not all iron in foods are created equal. Some are more available or better absorbed than are others.

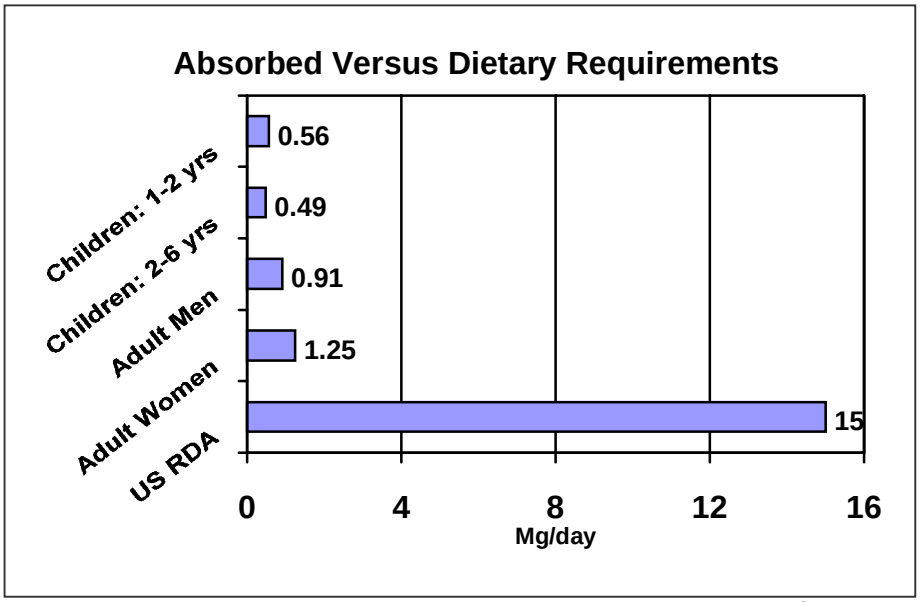


Figure 1a

The quality component of the equation is loss. Certain persons require more iron than do others. Women require more iron mainly because of menstrual blood loss. A body that is growing rapidly has higher iron requirements. Therefore, infants and young children or pregnant women carrying a growing fetus require more iron. In developing countries there is also iron deficiency due to pathological losses. A large part of the

population often suffers from a hookworm infection, which causes blood loss in the gut and significantly increases the requirement for iron.
Four dietary factors largely determine iron nutrition. The first is quantity or simply how many milligrams of iron per gram of food are consumed. Second, the nature or bioavailability of the iron compound in food is critical. Some forms of iron are much more available to the body than others. Third, there are promoters of iron absorption such as vitamin C or protein from animal products. Finally, there are substances that can inhibit iron absorption in the intestine such as phytates from grain products or tannic acids from tea. From a dietary perspective, iron status is determined by all these factors, not just the iron intake quantity.

Animal sources are the better iron sources because so-called heme iron, which comes from animal tissue, is much more easily absorbed than non heme-iron, which comes from vegetable or fortificant sources. On average, 15-20% of this heme iron can be absorbed in a meal. By contrast, non-heme iron is absorbed at a rate of only 2-5%. One of the principle reasons for the high prevalence of iron deficiency in the developing world is lower consumption of food from animal sources. This is the major contributory factor to iron deficiency anemia (IDA) in poor countries.

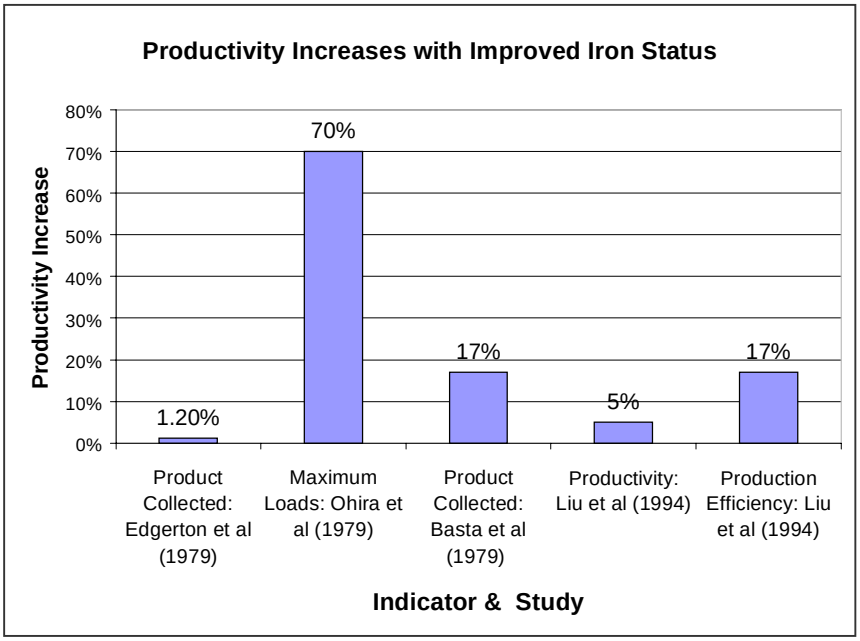
Populations that cannot afford iron rich foods because of economic constraints and who thus have a low intake of food from animal sources, are usually deficient in other major nutrients such as zinc, calcium and vitamin A. Effective interventions to reduce iron deficiency in developing countries need to consider iron deficiency not as a single nutritional deficiency but as part of multiple nutrient deficiencies. In contrast, in the U.S., where populations with very high requirements still suffer iron deficiency, the overall diet is usually adequate and there are no other deficiencies.

The Consequences of Iron Deficiency Anemia

When anemia is severe, sufficient oxygen cannot be carried to body tissues. This can lead to death. In South Asia and Africa, severe anemia can be fatal for pregnant women and children with serious infections or high fevers. Although in many parts of the world anemia is not solely caused by iron deficiency, iron deficiency usually plays a major role.

Specific consequences for young children are well established. These include a reduction of growth, development, and learning capacity. In essence, iron deficiency affects the brain to a degree similar to that of lead poisoning—reducing IQ or developmental quotient by an average of 5-7 points. Deficiency in iron can also cause the body to increase absorption of heavy metals such as lead. Therefore, it is a contributing factor in many cases of lead poisoning. There is also increasing evidence that suggests IDA reduces resistance to disease. In developing countries this can contribute to a range of severe consequences related to infection.

Among pregnant women, who have the highest requirements for iron, consequences of iron deficiency include increased probability of death during childbirth as well as pre-term delivery—babies born too early and too small. Furthermore, there is a direct association between babies born to iron deficient mothers and babies becoming iron deficient themselves.



From some perspectives, the population most significantly impacted by IDA in developing countries is average men and women. Iron deficiency in adults causes reduced muscular function and endurance. As a result, average men and women can not work as hard or as long. This directly lowers income and productivity. Economic output can drop an estimated 10-15% among iron deficient adults. Particularly in developing countries where physical labor represents a large segment of the overall workforce, this means a significant impact at the community and population level. One can conservatively estimate a 2-3% drop in total economic output. For a large country such as China or Indonesia, that equates to billions of dollars lost annually. (See Figure 1b).

Strategies to Control Iron Deficiency Anemia

There are two general strategies to control iron deficiency anemia. One is to improve iron intake by dietary means. The other is to work through the primary health care system to provide supplements, education and deworming.

Figure 1b

There are two major dietary approaches. The first focuses on proper education: teaching people how to select food items and to consume more iron rich foods. Second, through iron fortification or some other process—reducing inhibitors, increasing enhancers or fermentation, for example—the bioavailability of the iron in the diet can be improved. These strategies have distinct limitations and difficulties. In fact, we are far from the achievement of international goals, such as the World Summit for Children's goal of reducing iron deficiency anemia by one-third.

Nutrition education approaches are limited because iron-rich food from animal sources is often unaffordable to those at greatest risk. Meat products are usually

among the most expensive classes of food in any culture or society. There is evidence to indicate that most poor families will consume more meat products if their marginal income increases. It appears that the major role for nutrition education to play is helping the family identify inexpensive plant sources that are relatively rich in iron and enhance iron absorption. However, even with the knowledge of iron bioavailability from laboratory studies, there have been no small-scale trials or programs demonstrating that this approach is indeed effective. In the absence of evidence of efficacy or effectiveness, it would be difficult for a program- oriented agency such as UNICEF to recommend the use of a nutrition education-based approach as the sole intervention to improve iron nutrition.

Iron supplementation programs focus on the highest risk group, mainly pregnant women. This approach is limited by a number of factors. It does not address other sectors of the population that are also impacted, such as young children. Moreover, in many developing countries, iron deficiency is so severe prior to pregnancy that even proper supplementation during pregnancy may not be adequate—a case of too little, too late. In small-scale research trials, iron supplementation consistently reduced maternal anemia and hence demonstrated efficacy. However, in large-scale program settings, a number of evaluations failed to prove a significant reduction in maternal anemia—the prevalence remained high. It appears that there are a number of operational factors, such as supply, distribution, and the role of health workers, that must be properly addressed if iron supplementation systems are to work.

Feasibility of Iron Fortification

Fortification is a feasible approach to prevent iron deficiency on a population-wide scale for a number of reasons. First, technical feasibility has been well established. For example in North America, flour has been fortified with iron and other vitamins and minerals for over 50 years. Second, the cost of fortification is relatively low. Third, there is evidence from several parts of the world that iron fortification is effective. Fourth, once established, iron fortification does not require any special investment in pro-

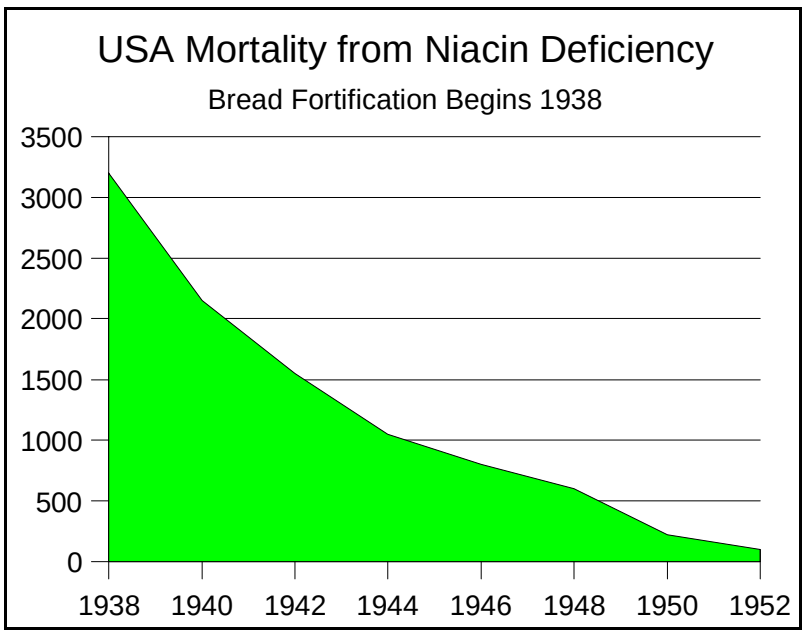


Figure 1c

motion or education. People do not need to know about fortification to benefit from it. Finally, since iron deficiency in the developing world usually coexists with a complex of nutrition deficiencies, flour fortification is attractive because it can deliver other vitamins and minerals, including zinc, vitamin A.

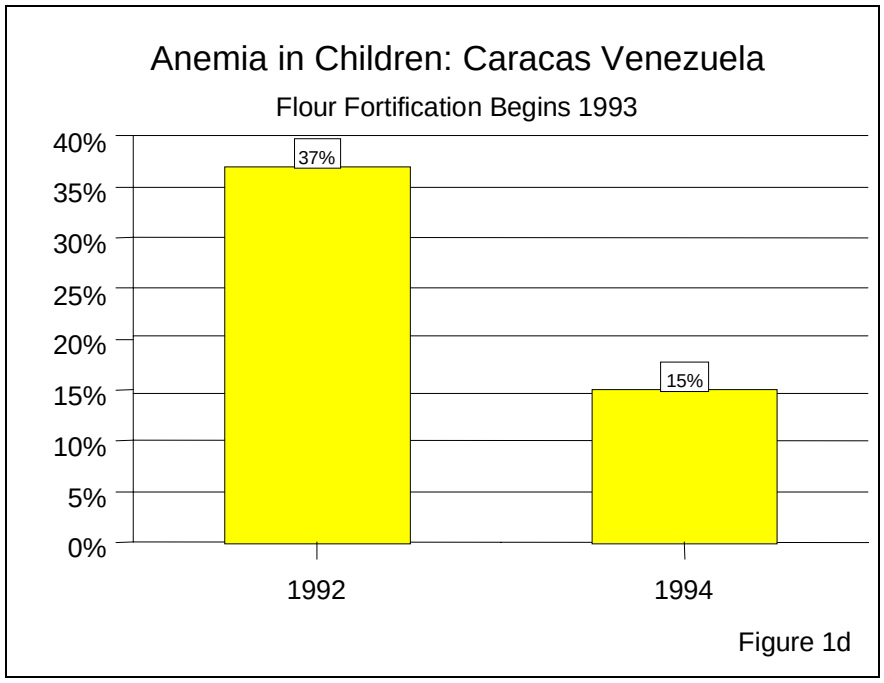
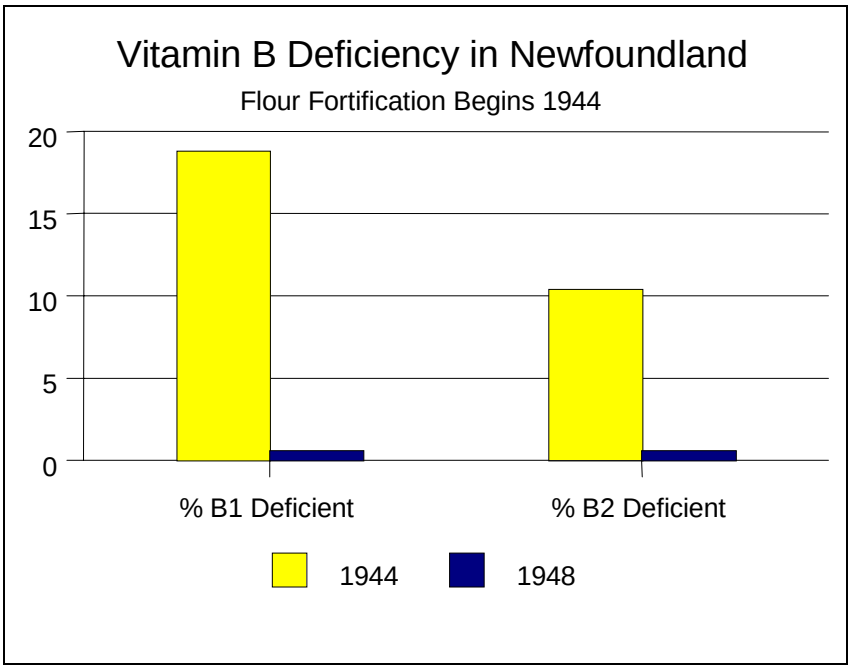


Figure 1d

There are numerous examples of fortification dramatically reducing rates of iron deficiency and anemia. Over 20 years ago in Chile, after receiving iron fortified milk powder, iron deficiency among low income children dropped from 38% to 9% and anemia from 23% to 4%. At one point, only 10% of infant formula was fortified with iron in the United States. After fortification became widespread, iron deficiency among infants dropped from 30% to less than 5%---the same prevalence found in older children and adults. More recently, in 1993, Venezuela made the decision to fortify all wheat and corn flour. Within one year, a survey of school aged children in Caracas slums showed a dramatic decline in iron deficiency from nearly 37% to less than 15%. Anemia prevalence dropped from about 16% to about 9%. (See Figure 1d).



Significant barriers and limitations accompany opportunities for iron fortification programs. An iron fortification program requires multiple partners, many of them beyond the traditional health and nutritional sector. For example, food producers—the private sector—are not usually involved with nutritional deficiencies. Defining who pays for fortification during start-up often presents a major barrier. Even though the cost of fortification is relatively low, it still exists and someone must pay for it. (If at all possible, the small additional cost should be borne by consumers to assure sustainability of the fortification program). In cases where a single food vehicle cannot reach all sectors of the population, some will argue that any fortification program should be deferred until a universal vehicle is identified. However, it is better to reach a substantial portion of the population than to not reach any at all. These obstacles often keep fortification from moving forward. Nevertheless, many countries overcome these obstacles and implement successful iron fortification programs.

Development of Iron Fortification of Wheat Flour in Indonesia

Indonesia is aiming for full national fortification of wheat flour by the end of 1998. In reviewing the development of this program, we can identify strategies to persuade governments and the private sector to take action.

The initial situation was not very encouraging. In Indonesia, average flour consumption is only about 15 kg per person per year while the consumption of rice is more than 110 kg per person per year. Because of the relatively low consumption, many insisted that flour fortification could not have a widespread impact and argued that efforts should be focused on rice. However, for a number of technical reasons, it is not feasible to fortify rice. A major obstacle to rice fortification in Indonesia is the decentralized nature of the industry. On the other hand, 5 large mills process all of Indonesia's wheat flour. One mill refines 85% of the wheat flour for the entire country. Moreover, consumption of noodles, a wheat product, is becoming increasingly widespread and penetrating even the most poor and rural areas. In light of this industry environment and the market situation, the government was convinced that flour fortification was feasible and could impact less advantaged and at-risk groups.

A fortification profile was developed with recommended levels of 6 mg/100g of iron, 3 mg/100g zinc, 400pg/100g riboflavin, 250pg/100g ppm thiamin and 200 pg/100g folic acid. The iron level is higher than the 48 ppm for flour in the United States. At this level, one packet of instant noodles, which is the most common unit of consumption and contains about 75 grams of wheat, can supply between one-quarter and one-third of the RDA for all these nutrients. Since fortification is a dietary approach, the goal is not to supply 100% of RDA with one pack of noodles. People consume other foods containing iron and sometimes more than one packet of noodles a day. However, just one meal of fortified noodles a day can make a big difference in meeting iron requirements.

The small incremental cost was a most difficult barrier to overcome in Indonesia. Adding 150 grams of recommended premix to one metric ton of flour adds US $1.30 to the cost of each ton of flour. This represents less than one-half of one percent of the cost of a ton of flour. Nevertheless, on a large scale, the cost can be daunting. Fortifying all the flour in Indonesia will cost about $4.6 million per year.

In Indonesia, a number of calculations were made that put a positive perspective on the cost of fortification. When advocating an increase in the cost of a staple food, no matter how small, one has to consider the additional expense or burden on the consumer. Fortification was calculated to add about 0.13 cents or 10 rupiah to the cost of a kilogram of flour. Since the smallest coin in Indonesia is 25 rupiah, 10 rupiah became a powerful figure illustrating the low cost. In retrospect, the 10 rupiah figure was crucial in convincing the Indonesian government to support the program.

Incremental costs can be framed in a number of ways to emphasize the low cost to consumers. For an average consumption of 15 kg per year, the annual increase was projected at about 1.5 cents or 150 rupiah per year. This adds 0.8 rupiah to the cost of a single packet of instant noodles, bringing the total cost to 400 rupiah. Such cost calculations made the added cost mentally easier to accept. Everyone can agree that is a reasonable burden to impose, especially considering the nutritional benefit.

Calculations were also made to project the potential impact on productivity. Assuming the average intake of 15kg fortified flour per person per year, the recommended 60 mg per kg of flour translates into an additional annual intake of 900 mg per year. This is equivalent to providing 30 mg iron tablets every day for 1-2 months. This dosage has been shown to correct iron deficiency among women and children. So even though some people argue that Indonesia may not have high flour consumption, on average, current consumption can deliver a significant amount of iron.

It was projected that halving iron deficiency among women, from 25% to 12%, would result in an average increase in work productivity of 10% for those women who were no longer anemic. This productivity gain among the 12-13% of women whose deficiency was corrected through fortification translates into an annual gain of 15,000 rupiah—or a 0.5% rise in Indonesia's per capita GDP of 3 million rupiah. Since the average annual cost increase for fortified flour is 150 rupiah, the cost-benefit ratio of flour fortification is 1:100 for Indonesia. That is another very attractive figure.

Advocacy for flour fortification in Indonesia involved answering questions about safety. There is always concern about excess iron in the diet. Fortunately, iron absorption is a well-regulated process. Iron deficient individuals absorb more iron while those without deficiency absorb far less. There is no question that people who do not need iron will absorb a bit more iron from fortification. However, the body also has a remarkable capacity to store extra iron, making it unlikely the additional iron will reach a harmful level. The main exception is the potential harm to the few people per thousand who suffer clinical conditions that would cause high iron ab-

sorption and ultimately iron overload. Thus far, the vast experience with iron fortification in developed countries has not shown any evidence suggesting that these individuals are harmed by greater dietary iron supply. There is sufficient evidence to indicate that the protection of individuals with iron overload condition is best done through clinical screening and treatment. Reducing or withholding iron supply in the diet on a theoretical basis is unlikely to protect those with an iron overloading condition, yet it deprives those who can benefit from the correction of iron deficiency anemia.

Summary

Fortification is a feasible strategy to reduce iron deficiency in many countries. There is ample evidence of its public health impact and cost-effectiveness. Moreover, these benefits can be multiplied efficiently because the same fortification process can add other needed nutrients to the diet. Establishing flour fortification creates a means to prevent an array of nutritional disorders that often coexist with iron deficiency.

Fortification should not be viewed as the only strategy to control iron deficiency anemia. Reducing iron deficiency during pregnancy is not possible through fortification alone. In fact, no single approach, by itself, can eliminate iron deficiency. Thus, the current effort invested in supplementation of high-risk groups must be continually improved (although eliminating IDA in infancy is possible depending on the nature of the diet). However, fortification can definitely improve baseline iron status for the population and eliminate the deficiency among school age children and non-pregnant women. As economic development raises incomes and enables more people to afford iron rich foods, dietary diversification will become more feasible. Fortification should be pursued while using all strategies in a synergistic fashion.

Iron Absorption, Bioavailability, and Possible Risks of Iron Fortification

Sean Lynch
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Iron Absorption & Bioavailability

The adult human body contains three to four grams of iron. It is an essential element involved in oxygen transport and storage, cellular oxidative metabolism, cell growth and division and many other biochemical processes. It is also potentially very damaging to cells because it can promote free radical formation. Under physiological circumstances, body iron is efficiently harvested and re-utilized when cells die and total body iron is held within narrow limits. A small amount of iron is lost through the skin, from the gastrointestinal tract, and the urinary tract and as a result of menstrual bleeding. When compared with the total body iron, the quantity of iron lost is very small—approximately 1 mg/day for a man and 1.5 mg/day for a woman.

Iron balance is achieved by adjusting the rate of absorption to meet this loss as well as provide for the requirements for growth in children. Absorbed iron intake requirements are therefore approximately 1 mg/day for men and 1.4 mg/day for women. The total daily requirement for children rises from about 0.5 mg to 0.8 mg during the first decade of life—a proportionately high requirement given their smaller body size and food intake.

In normal human beings, the mucosal cells of the upper gastrointestinal tract adjust the rate of absorption to allow the body to accumulate a little more iron than is needed for its functional requirements. This iron enters the body's iron store. However, the rate of iron absorption is rapidly curtailed as the size of the iron store increases, preventing the accumulation of unnecessary and potentially harmful quantities of iron by the body. The ability of the absorptive mechanisms to prevent the absorption of iron when iron stores are sufficient is extremely important since the human body has no physiological mechanism for increasing the rate of iron excretion. On the other hand, if the requirement for iron is increased (growth, pregnancy, blood loss), the iron store is utilized first—prior to the body's increasing absorption. As the size of the iron store decreases, the rate of absorption rises. Individuals eating a Western diet can increase iron absorption four-to five-fold once all the storage iron has been used.

The ability of the absorptive mechanisms to finely regulate iron absorption, under all but the most extreme circumstances, would ensure strict iron balance if the dietary iron supply was always adequate and present in an easily assimilable form. However, this is not always the case. In reality several other factors play a crucial role. They are:

a. The quantity of iron in the diet. Iron is well distributed among different foods. Food iron intake is therefore related to caloric intake. The iron content of typical Western meals is about 6 mg/1000 calories. Iron intake is several times higher than the iron requirement. In the United States, normal adult men maintain iron balance by absorbing about 6 % of the iron they consume while normal adult women absorb about 15% because of their greater requirements and lower caloric (and therefore iron) intake. Young children also need to absorb 10-15% of the iron they ingest to meet the requirements for growth and expansion of the red cell mass. In some countries iron intake is lower because major staples such as low extraction wheat flour or polished rice, provides less iron. Even in these situations dietary iron intake exceeds daily requirements.

b. The chemical form of the iron. Iron that is insoluble in gastric juice is not absorbed. Soluble food iron exists in one of two forms: heme iron that is derived from hemoglobin and myoglobin in meat (the iron remains as part of the porphyrin complex which is absorbed intact into the mucosal cells), and nonheme iron which is the soluble elemental iron extracted from all other iron containing compounds. The heme iron in meals is always very well absorbed and is a very dependable source of iron for preventing iron deficiency. Heme iron constitutes only a small fraction of the iron even in Western meals. Nevertheless, because of its high bioavailability it makes a significant contribution to the amount of iron absorbed.

c. The composition of the meal. There are two major reasons for the high prevalence of nutritional anemia in developing countries. First, iron requirements may be increased by disorders such as hookworm that cause pathological blood loss. Second, most, if not all of the dietary iron is in the nonheme form. The body has considerable difficulty in extracting nonheme iron from many vegetable and grain diets because certain chemical compounds in food inhibit absorption. Therefore in many developing countries, even though the intake of dietary iron from whole grains is quite high, the amount absorbed is actually quite low.

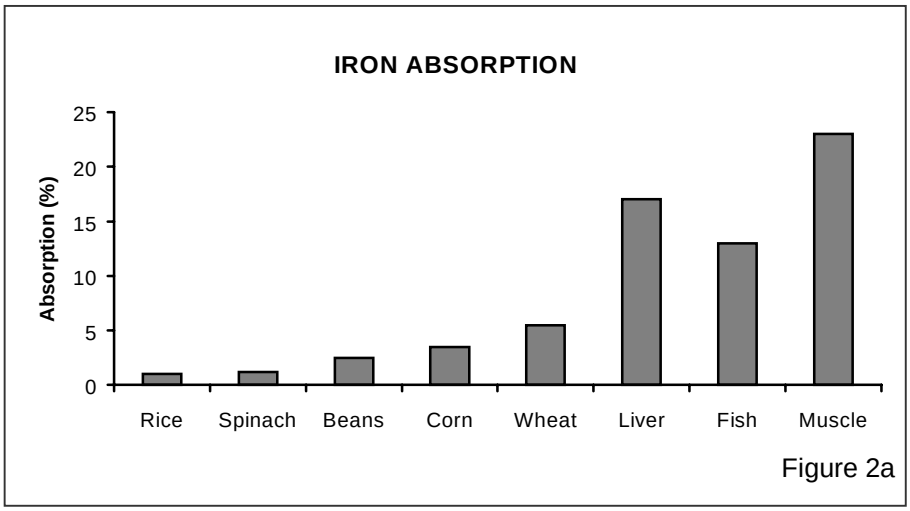

Figure 2a

Measuring Iron Absorption

Our understanding of iron absorption and the modifying role of meal composition was facilitated by the discovery of simple techniques for measuring iron absorption

in human beings. (See Figure 2a). Radioisotopes of iron were used in the earlier studies. In both normal and iron deficient individuals, eighty percent or more of any absorbed iron is present in circulating red blood cells two weeks after it is ingested. Therefore, absorption can be measured readily in relatively large numbers of individuals by offering radioactively tagged meals and assaying the radioiron content of a blood sample two weeks later. Similar techniques are now being employed utilizing stable isotopes.

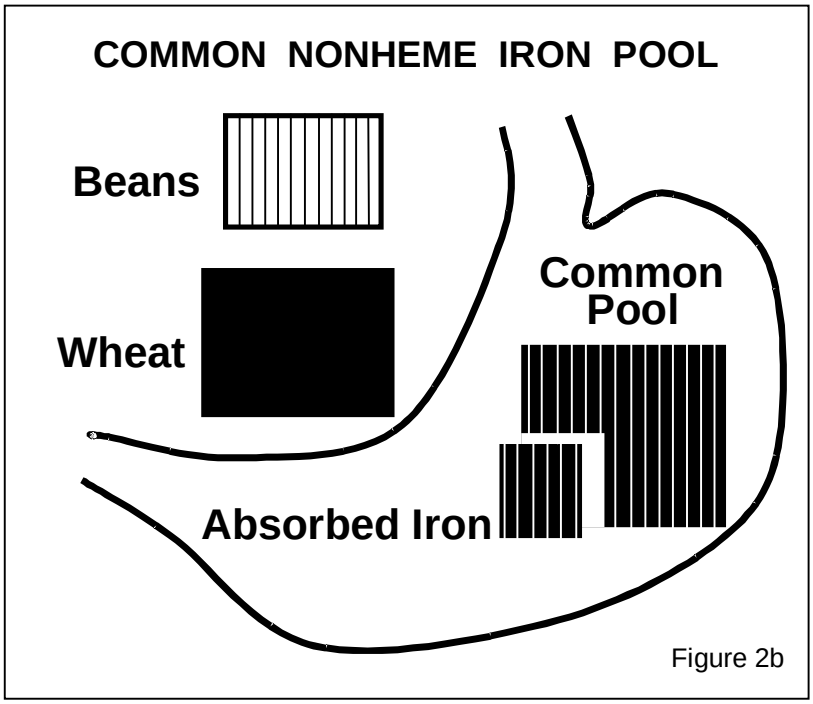

Figure 2b

The early studies of dietary iron absorption were based on foods that were prepared from plants grown in hydroponic culture media containing radioactive iron or animals that had been injected with radioactive iron (intrinsic labeling). The investigators could therefore be reasonably certain that measured absorption was really representative of actual food iron absorption. There was an extraordinary range in terms of the percentage of iron absorbed from different foods. Iron in vegetables and grains was relatively poorly absorbed, ranging from about 1% for rice to 5-6% for wheat. Iron from meat was absorbed much more efficiently, between 10-20%.

It would have been very difficult to measure absorption from every single different kind of food. Fortunately, an important characteristic of nonheme food iron absorption has been discovered. If two foods with markedly different absorption values for iron were labeled with different radioiron isotopes and mixed in the same meal, the absorption of both radioiron isotopes was the same and lay somewhere between the two extremes. Therefore, it became evident that when several foods are eaten together in the same meal, soluble nonheme iron destined for absorption behaves as though it is derived from a single common pool formed in the stomach and duodenum. (See Figure 2b). Absorption from this pool is determined by the combination of factors that affect iron absorption present in the whole meal. Fortification iron enters this pool and is subject to the same influences as the nonheme iron naturally present in the food.

Factors Affecting Absorption

Many of the most important factors affecting iron absorption (bioavailability) in mixed meals have been identified. (See Figure 2c). Absorption is improved by ascorbic acid, other organic acids, and animal tissues. Ascorbic acid has a concentration dependent

effect: the more ascorbic acid present, the greater the effect. Animal tissue, on the other hand, improves absorption by a factor of about two only if present in sufficient quantity.

Major inhibitors of absorption are found primarily in vegetable foods and beverages such as tea and coffee. They include phytates, polyphenols and vegetable proteins. Proteins derived from sources other than animal tissues, e.g. milk and egg proteins are also inhibitory. It is important to note that the major inhibitors in vegetable meals, phytates and polyphenols have a very significant effect even in fairly low concentrations.

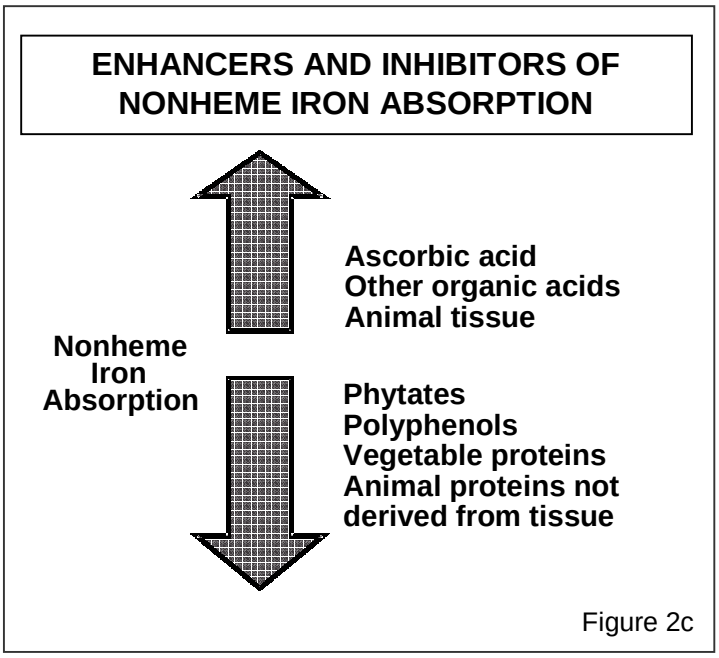

Figure 2c

As a result of the presence of these dietary compounds, typical diets eaten in developing countries consisting primarily of cereals, roots or tubers, and legumes—with negligible quantities of meat, fish and ascorbic acid rich foods—result in low bioavailability (approximately 5%). Diversified diets eaten in Western countries containing generous quantities of meat, poultry, fish and foods containing ascorbic acid are much better sources of iron (approximately 15% average bioavailability).

Iron Fortification: Selection of Iron Compound for Food Fortification

Fortification is the process of adding nutrients to food to improve the quality of the diet. One justification for fortifying milled cereals is to replace the nutrients lost in the milling process. However, in countries where iron deficiency is highly prevalent, iron fortification is viewed as a means of delivering additional bioavailable iron. Iron fortification of food is considered to be the most efficient and cost-effective method for improving the iron nutrition at a national population-wide level.

There are several technical constraints that limit the addition of any particular iron compound to many foods. They will not be dealt with here. The following discussion will deal only with the importance of using a bioavailable iron compound and of ensuring that adequate bioavailability is maintained in the real meal settings. Although it is possible to fortify food with heme iron, technical difficulties have prevented its implementation outside experimental trials. Fortification therefore entails the use of a bioavailable iron salt or iron chelate.

To be effective, an iron compound must be soluble in human gastric juice. Ferrous sulfate is freely soluble in water and gastric juice. It is the cheapest and most widely used iron salt for food fortification. It is customary to characterize the bioavailability of other iron compounds by comparing their bioavailabilities with ferrous sulfate. Designated relative bioavailability (RBV) is derived from experiments in which the absorption of an iron compound is compared with ferrous sulfate (RBV of ferrous sulfate = 100%). The average RBVs for a few iron compounds that have been considered as iron fortificants are given in Table 1. Results based on human studies are considered to be the more reliable. To be effective, an iron compound chosen for fortification must have an RBV comparable to ferrous sulfate as measured in human studies.

Table 1

Relative Bioavailability of Iron Sources Commonly Used in Food Fortification

Iron Source	Average Human RBV(%)
Iron Salts Freely Soluble in Water	
Ferrous sulfate	100
Ferrous gluconate	89
Ferrous lactate	106
Poorly water soluble	
(soluble in gastric juice)	
Ferrous fumarate	101
Ferrous succinate	123
Elemental Iron	Variable[1]

[1] Depends on particle size, surface area and common nonheme pool acidity in the stomach

Iron Fortification: Bioavailability of Fortification Iron from Meals

The selection of an iron compound that has an adequate RBV as well as the appropriate chemical properties to allow for its incorporation in the target food vehicle is only the first step in designing an effective food fortification strategy. As described above, fortification iron enters the common nonheme pool. Even an iron salt that is freely absorbed when taken without food may be ineffective when added to certain meals. Inhibitors in the meals may prevent all but a small fraction of iron from being absorbed. It is therefore essential to evaluate the bioavailability of the potential fortificant in the context of the meals in which it is to be consumed.

The bioavailability of iron added to meals has usually been estimated on the basis of radio or stable isotope studies in human volunteers. As indicated above, the absorp-

tion of iron in these individuals will vary depending on their physiological absorptive capacity, which is in turn dependent on the size of their iron stores. An individual with adequate iron stores will absorb relatively little iron even if highly bioavailable iron is supplied because the absorptive mechanisms are regulated downward.

When measuring iron absorption, the effect of differences in iron status among different subjects must be accounted for since this is a major determinant. This can be accomplished by measuring the absorption from a standard dose of a highly bioavailable iron salt (ferrous sulfate given with ascorbic acid) given after an overnight fast. A standardized bioavailability measurement can then be obtained by making a correction based on the reference dose absorption. Customarily, absorption values are calculated for a reference dose absorption of 40% which was found to be the approximate value obtained in most individuals with absent iron stores, but not anemia.

A large body of experimental evidence obtained over many years indicates that the mere addition of iron to common foods in developing countries is unlikely to have significant impact on iron status. In addition to adding dietary iron, it will be necessary to improve the bioavailability of the iron. From a theoretical point of view, this can be done in a number of ways. Bioavailability can be improved by removing inhibitors from the diet. This could involve a combination of dietary education to reduce the intake of tea or coffee with meals as well as technological approaches to lowering the levels of these substances in foods. However, it will be necessary to reduce the concentrations of the important inhibitors, phytates and polyphenols, to very low levels.

Additional animal tissue in the diet would be a very effective approach. This is not a pragmatically feasible solution because of the cost and, in some cases, the dietary practices and religious beliefs of the people at risk. Alternatively, enhancers could be added. Ascorbic acid is a very attractive option. Bioavailability is improved over a wide range of values depending on the molar ratio of ascorbic acid to iron in the meal. It has been very effective as an additive in infant formulas in Western countries. However, it is relatively expensive and unstable if submitted to prolonged storage in unsealed containers or used in foods that need to be cooked. For a number of reasons, the options outlined above may not be currently realistic to improve population-wide iron status in developing countries.

The search for alternative ways of improving bioavailability continues. Recently there has been considerable interest in ethylenediaminetetraacetic acid (EDTA). EDTA can be added to many foods in small quantities either as sodium iron EDTA or sodium EDTA. It has a major advantage over ascorbic acid in that it is stable during storage and cooking. EDTA interacts with the common nonheme iron pool, releasing iron from inhibitors such as phytates and making it available for absorption. The EDTA itself is only absorbed to a very small extent. However unlike ascorbic acid, the improvement in absorption is limited to a two-to three-fold increase. Moreover, the range of effective molar ratio (approximately 1:1, EDTA; Fe, a little less) is narrow and is critical to ensuring effective enhancement of iron absorption.

Possible Risks Associated with Universal Iron Fortification in Western Countries

The prevalence of iron deficiency has fallen dramatically in Western countries over the last few decades. There is little doubt that iron fortification of foods has played a significant role in this important achievement, particularly with respect to infants and young children. Every effort should be made to achieve similar improvements in the nutrition of individuals in the developing countries. However, an awareness of possible risks of a high iron intake by individuals whose iron requirements are low (men and postmenopausal women) has been stimulated in the United States in recent years by three sets of observations.

a. The demonstration that mean serum ferritin concentrations appear to have increased significantly in the years between the last two National Health and Nutrition Surveys (NHANES II, 1976-1980, and NHANES III, 1988-1994) in all groups of individuals.
b. The observation that, in a carefully conducted epidemiological study carried out in Finland, there was a relationship between high serum ferritin values and the risk for ischemic heart disease.
c. The discovery of a point mutation in the HFE gene (C282Y) that is very common among people of Celtic descent living in Europe, the United States, Australia and South Africa who have hemochromatosis. Over 90% of individuals with phenotypic hereditary hemochromatosis in these population groups are homozygous for this mutation. Recent studies have demonstrated that the homozygous state for this abnormal autosomal recessive gene occurs in at least 1 in 300 individuals with a 1 in 20 heterozygous carrier state. Currently, it appears to be very rare in other ethnic groups studied. Homozygotes are at risk for developing clinical hemochromatosis which is a life threatening clinical disorder characterized by cirrhosis of the liver, primary liver cancer, heart failure, diabetes, damage to other endocrine organs (particularly the pituitary gland), arthritis and skin pigmentation. Heterozygotes accumulate iron stores that are somewhat higher than age-and gender-matched unaffected members of the same population, but do not suffer any harmful consequences.

There is currently no convincing evidence that demonstrates a clear relationship between modestly increased iron stores and clinical disease. Attempts by others to confirm the putative relationship between the size of iron stores (based of serum ferritin concentrations) observed in Finland have yielded conflicting results.

The reasons for the observed increase in serum ferritin concentrations in the HANES III remain uncertain. Factors other than storage iron status may play a role in determining serum ferritin concentrations. It is nevertheless possible that this finding does indeed indicate increasing storage iron status in American men and postmenopausal women. If the latter proves to be the case, it will be very important to discover the rea-

sons and to reverse any trend in this direction. There is no known benefit of having increased iron stores.

One recently reported study, "The Framingham Heart Study," does provide some helpful preliminary information. Ferritin values were higher in men than in women, but did not show an increase with age in these elderly individuals which suggests that there was no progressive rise in iron stores. There was a direct correlation between serum ferritin values and the intake of heme iron, dietary ascorbic acid and iron supplements. Higher ferritin values were also positively correlated with alcohol intake and negatively with coffee consumption. This study demonstrates the potential complexities in dealing with the higher ferritin values recorded in HANES III.

The relationship between dietary iron intake (both quantity and chemical form) and the phenotypic expression of genotypic hereditary hemochromatosis will be the subject of careful study in the coming years since it is now possible to identify individuals carrying one or both mutated genes for the disorder. However, at the present time there is no reason to believe that food fortification with iron significantly affects the size of iron stores in heterozygous individuals. Dietary manipulation has not been shown to play a useful role in the management of the clinical disorder which is customarily treated by the removal of iron by repeated phlebotomy. The current emphasis in dealing with this eminently treatable condition is on early detection and the institution of a program of regular phlebotomies to remove the excess iron and prevent further iron accumulation.

Summary

The cost-effectiveness and the scientific basis of implementing iron fortification is well established. Nevertheless, further research in a few areas remains an urgent necessity. The most important of these is the search for optimal methods for improving food iron bioavailability. The efforts of nutritionists involved in eradicating nutritional iron deficiency anemia should focus on the implementation of fortification programs that are based on the available scientific information relating to iron absorption and iron bioavailability. Concerns about the possible effects of iron fortification on the prevalence and severity of iron overload in vulnerable groups in Western societies should not delay the implementation of fortification in developing countries.

Optimizing Iron Compounds And Bioavailability

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Swiss Federal Institute of Technology

Stages in the Development of an Iron Fortified Food

For several reasons, iron is the most difficult mineral to add to foods while ensuring adequate bioavailability by the body. Iron compounds that are highly bioavailable, such as ferrous sulfate, can cause color and flavor changes. These organoleptic problems raise issues of consumer acceptance. On the other hand, iron compounds that do *not* cause organoleptic problems, such as elemental iron, are not as bioavailable and are poorly absorbed. Finally, major vehicles for iron fortification contain potent inhibitors of iron absorption, such as phytic acid in cereals, or are often consumed along with foods that contain powerful inhibitors such as polyphenols in tea. Even highly absorbable iron compounds, such as ferrous sulphate, may be poorly absorbed unless food manufacturers protect the iron or remove the inhibitors from the food.

A three-stage process of development for iron fortified food products may help overcome these difficulties. The first stage, *optimizing the iron compound*, involves selecting an iron compound, which offers the highest potential absorption while causing no organoleptic problems. Optimizing the iron compound also involves organoleptic trials in order to identify problems with color or taste that may arise during storage or preparation. The second stage, *optimizing iron absorption*, involves assessing nutritional needs of the consumer; determining the target level of iron to be provided by a food product; and finally estimating or measuring actual iron absorption to determine whether those consumer needs are met. With these findings in hand one can evaluate options including the addition of enhancers, removing inhibitors or simply modifying the level of added iron. The third and final stage is *to demonstrate improved iron status* by monitoring a decrease in iron deficiency anemia among consumers.

Selecting the Iron Compound

The relative bioavailability of iron compounds is determined by their solubility in the stomach's gastric juice. The highly absorbable compounds, such as ferrous sulphate, gluconate and ferric ammonium citrate, are water soluble and dissolve instantaneously in the dilute acid of the gastric juice. Compounds such as ferrous fumarate, ferrous succinate and ferric saccharate, dissolve poorly in water but dissolve over time in the presence of dilute HCL. These can also be highly absorbable. On the other hand, the body has difficulty absorbing water insoluble compounds that are poorly dissolved in dilute acid. This category includes different forms of elemental iron, such as electrolytic, carbonyl and reduced iron, as well as the phosphate iron compounds, ferric pyrophosphate and orthophosphate. (See Figure 3a).

The relative bioavailability of iron compounds is standardized on a comparison to ferrous sulfate. Ferrous sulphate is given a relative absorption (RBV) of 100 in both rats and humans. Freely water soluble compounds also have a relative absorption of 100. Compared to ferrous sulfate, the iron compounds soluble in dilute acid indicate a rela-

Relative Absorption Common Iron Compounds

(Hurrell, 1997)

	rat	man	approx.relative cost
water soluble			
ferrous sulphate	100	100	1.0
soluble in dilute acid			
ferrous fumarate	95	100	1.3
ferrous succinate	119	92	4.1
ferrous saccharate	92	74	5.2
poorly soluble in dilute acid			
ferric pyrophosphate	45-58	21-75	4.1
ferric orthophosphate	6-46	25-32	2.3
elemental iron: electrolytic	44-48	5-100	0.5
carbonyl	39-66	5-20	1.0
reduced	24-54	13-148	0.2

Figure 3a

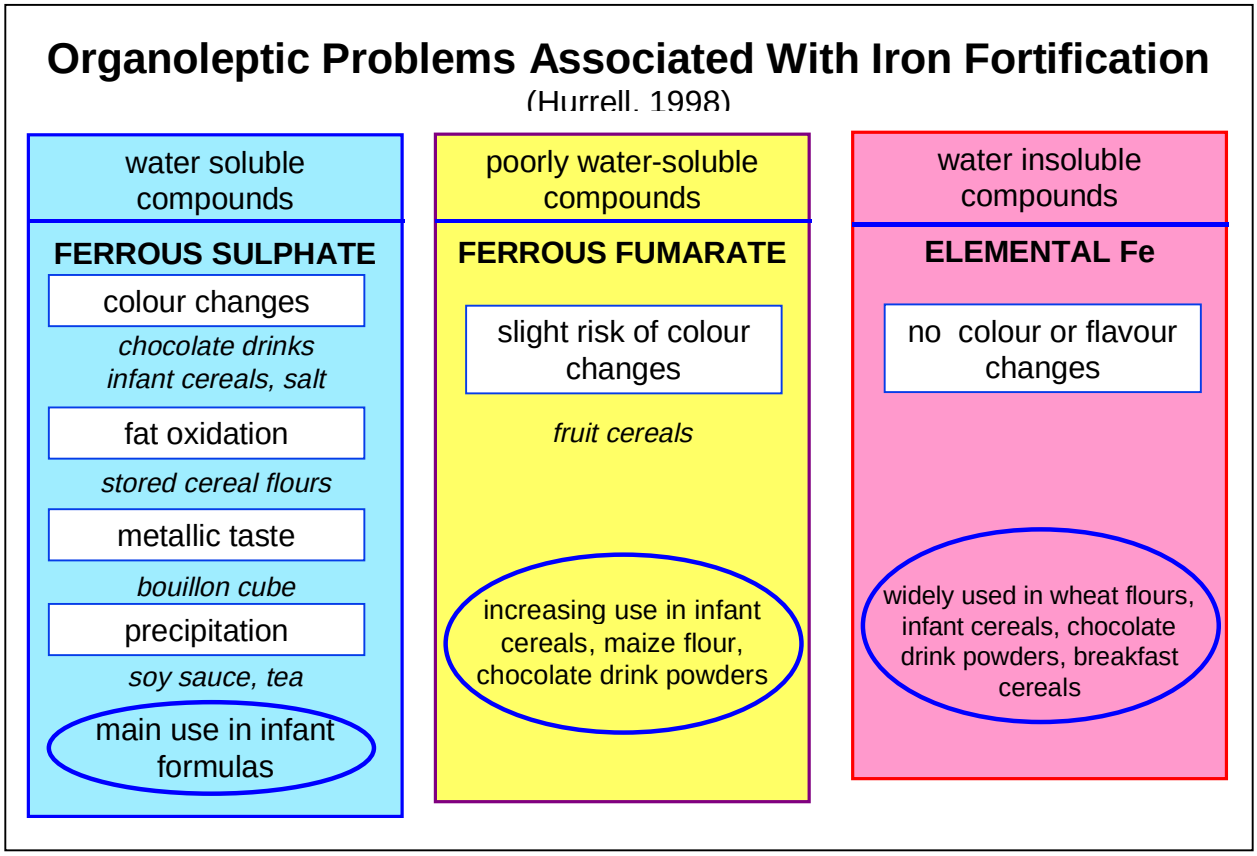
tively high RBV in humans: 100 for ferrous fumarate, 92 for ferrous succinate and 74 for saccharate. Compounds that are poorly soluble in dilute acid have low and variable RBV, varying from RBV of 21-75 for ferric pyrophosphate or 25-32 for ferric orthophosphate. RBV for the various forms of elemental iron varies more extremely from RBV of 5 to 148.

There are several explanations for this wide range of findings. Different batches of the same compound have somewhat different physiochemical properties and thus different solubility in the gastric juice. Although some experimental elemental iron compounds have shown higher absorption, it is highly unlikely that the higher values for elemental iron would occur in a commercial product. Commercial compounds that have been tested in rat assays all indicate an absorption about half of ferrous sulphate. Generally, relative cost factors for the various iron compounds are also standardized using ferrous sulphate. With the relative cost of ferrous sulphate at one, costs range from 4-5 for ferrous succinate to 0.5 for electrolytic and 0.2 for reduced iron.

Organoleptic Issues

There are a number of organoleptic problems associated with adding highly absorbable water soluble iron compounds to food products. Ferrous sulphate causes some unacceptable color changes. For example, chocolate drinks become gray, infant cereal with banana turns blue and salt can change to brown. Ferrous sulphate causes metallic off-flavors in bouillon cubes. It catalyzes fat oxidation reactions and consequently, cereal flours stored over a period time become rancid. When added to soy sauce, soluble peptides will precipitate. Ferrous sulphate in sugar causes a flocculation on the surface whenever the sugar is added to tea—as the polyphenols in the tea combine with the iron. In short, it is very difficult to add ferrous sulfate to foods without changing their organoleptic quality and threatening consumer acceptance. It is usually used only in infant formulas, short shelf life bread and some pastas.

As a result of these organoleptic difficulties, the poorly water-soluble compounds such as ferrous fumarate are increasingly used in fortification. Although there is a slight risk of color change, particularly in slightly acid products such as fruit cereals, it can be used in infant cereals, in maize flour and chocolate drink powders. The least absorbable iron forms, such as water insoluble compounds like elemental iron, produce no color or flavor changes. As a result these compounds are very widely used in fortification of wheat flours, infant cereals, chocolate drink powders and breakfast cereals. (See Figure 3b).



The impact of various iron compounds on rancidity in wheat flour can be measured using pentane as an indicator. Formation of pentane correlates with rancid off-flavors in flour. Ferrous sulphate, ferrous gluconate, ferric pyrophosphate and elemental iron were added to infant cereals made of pre-cooked roller-dried wheat flour and stored in aluminum cans at 37° C for up to one year. Pentane in the headspace of the cans was measured by gas chromatography. Pentane tests have demonstrated that cereals with water soluble iron compounds reached 30-40 ppm pentane within 30-40 days. On the other hand, the formation of pentane in cans of cereal with water insoluble compounds such as elemental iron was negligible and similar to the content with no added iron. (See Figure 3c).

Optimizing Absorption by Encapsulation

There are several alternatives to maximizing absorption while minimizing unacceptable organoleptic changes. These include encapsulating the iron, utilizing novel iron compounds, adding absorption enhancers, and the removal of absorption inhibitors.

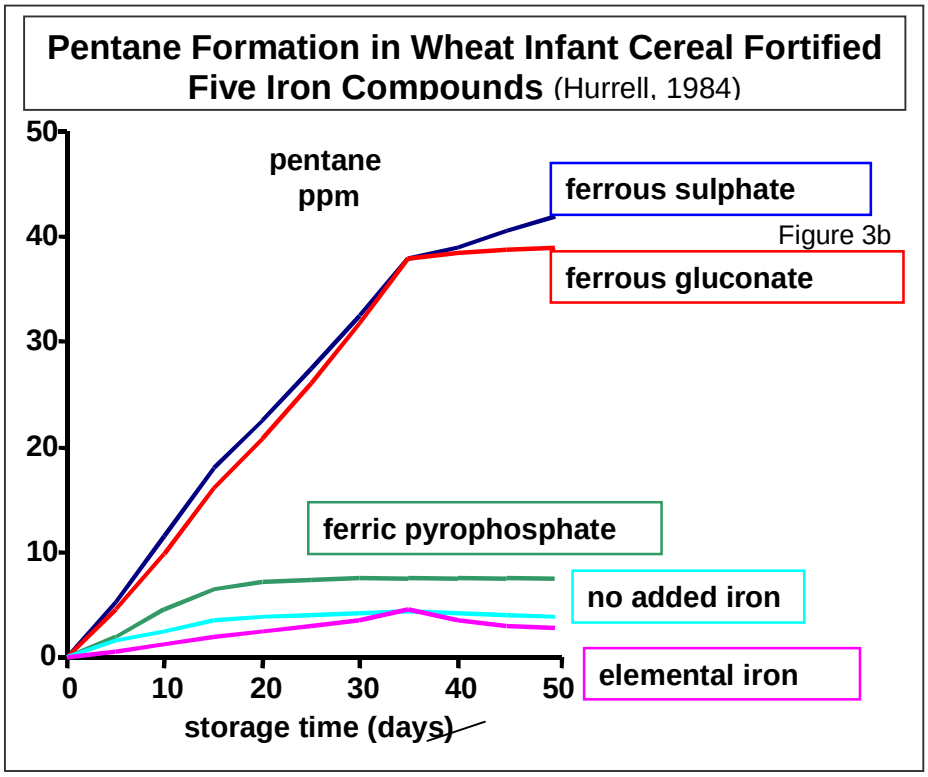


Figure 3b

Encapsulation, which prevents fat oxidation during storage of the cereal flours, involves coating the iron with a protective layer that does not affect its ability to dissolve in the gastric juice. In rat assays, coating with hydrogenated oil such as soy bean oil or with ethyl cellulose or maltodextrin had little effect on the RBV. However, the hydrogenated oils are not heat stable and melt at about 65° C while ethyl cellulose and maltodextrin are water soluble. When the coating is removed, unacceptable color changes follow. When adding hot water or milk to infant cereal, the fat capsulation melts and, if there are bananas in the cereal, the cereal turns blue. If a manufacturer is drying chocolate milk powder that includes an encapsulated iron compound, the dried powder turns gray. This lack of heat stability is a key barrier to iron encapsulation.

Figure 3c

More research needs to be undertaken in order to identify a capsule which is stable to heat and insoluble in water and can be removed during digestion so that the iron is bioavailable.

Optimizing Absorption with Iron EDTA

New or novel iron compounds such as Iron EDTA should be considered. Iron EDTA was accepted by JECFA 1993 for use in government sponsored food fortification programs. Although it is a soluble iron compound, and consequently can cause unwanted color reactions in certain situations, EDTA does not provoke fat oxidation during storage in cereal flours. No rancidity was reported in a number of studies with several different cereal flours, including wheat flour.

The superior relative absorption of EDTA has been demonstrated in many studies over the past 20 years. EDTA consistently indicates 2-3 times better absorption than ferrous sulphate, which is the best of the ordinary compounds. In an unpublished study in collaboration with Cook (1992, Kansas University Medical Center), it was found that adding iron EDTA to infant cereals resulted in a fourfold increase in absorption compared to ferrous sulphate and ferrous fumarate.

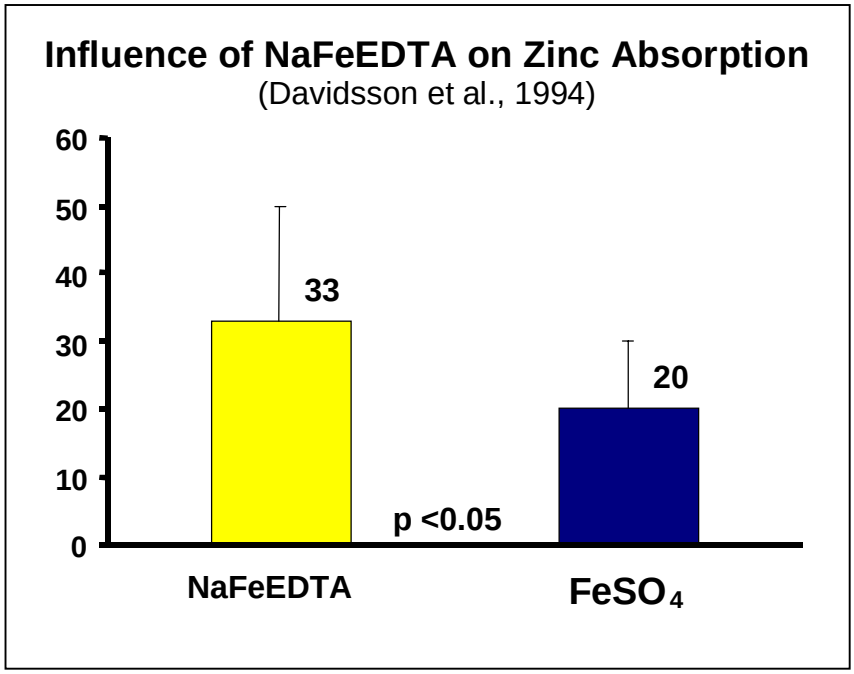


Figure 3d

This markedly superior absorption, however, is limited to high phytate meals because EDTA chelates the iron thus protecting it from phytates. When there is no phytate present, EDTA is similar or displays even less absorption than ferrous sulfate. In a sugar syrup for example, ferrous sulfate would be better absorbed than iron EDTA. But in a high phytate cereal, iron EDTA has an advantage of 2-4 times. Consequently, iron EDTA fortification of wheat and corn flours offers an opportunity to deliver iron to the at-risk populations in developing countries. However, cost remains an issue with EDTA as it is approximately six times more expensive than ferrous sulfate.

EDTA offers increased zinc absorption as well. In a 1994 study using stable isotopes, 10 women consumed high phytate wheat flour baked into bread rolls. The rolls con-

tained either 5 mg iron as ferrous sulphate or as iron EDTA. Zinc absorption was 33% with iron EDTA and 20% with ferrous sulfate. It is noteworthy that urinary excretion of zinc did increase slightly with iron EDTA but was nevertheless less than 1% of intake. (See Figure 3d).

Optimizing Absorption with Ferrous Bisglycinate

It has been suggested that another novel compound, ferrous bisglycinate, offers superior relative absorption because the glycine binds iron and protects it from inhibitors in a similar way to EDTA. However, this superior absorption has not been convincingly demonstrated in published literature. Fox et al. (1998) compared iron absorption in a vegetable puree and a whole grain infant cereal in two studies, one with ferrous sulphate and one with ferrous bisglycinate. The results are limited by the fact that the comparisons are not strictly between the iron compounds but rather paired within each study of vegetable and grain meals. Given this limitation, the study indicates 9% absorption from ferrous sulphate in the vegetable meal versus 9.8% for the glycinate. In the higher phytate grain meal, Fox et al. report 3.8% absorption from ferrous sulphate and 5.2% from ferrous bisglycinate, slightly higher but not significant. While the gain in absorption is minor, ferrous bisglycinate is a soluble iron compound, and like other soluble iron compounds, can cause color reactions and provoke fat oxidation. (See Figure 3e).

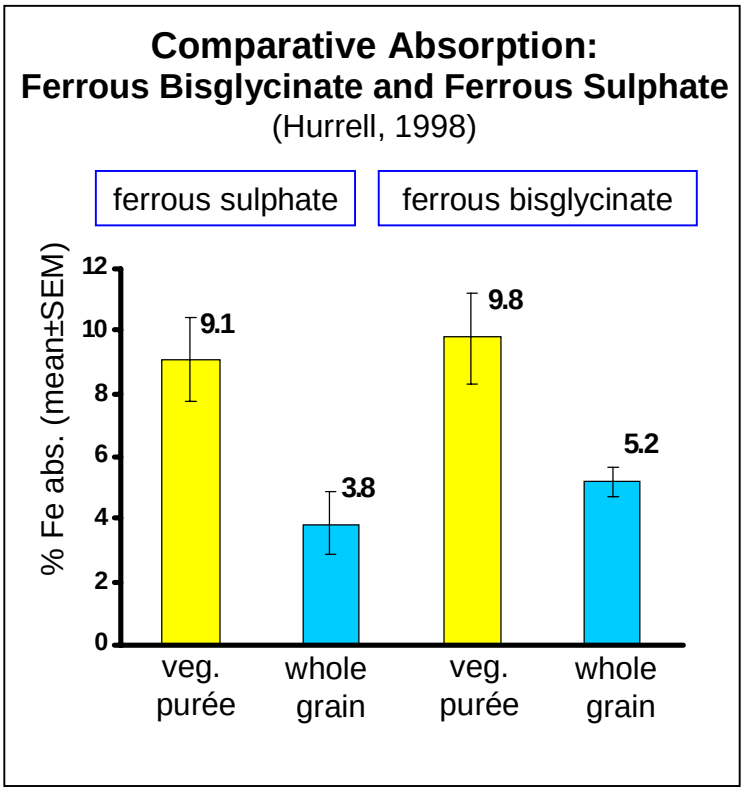


Figure 3e.

Optimizing Absorption with Ascorbic Acid

From the food manufacturer's point of view, adding ascorbic acid offers the easiest approach to optimizing absorption. A number of studies have shown that ascorbic acid increases absorption of all fortification iron compounds in humans. Using two iron compounds, Derman et al. (1980) reported significant increases in iron absorption from infant cereals. The increase was dependent on the level of added ascorbic acid and iron. In an infant cereal meal containing 6.9 mg iron from ferrous sulfate, absorption increased from 1% to 3.7% after adding 24 mg ascorbic acid. Absorption rose from 0.8% to 10.3% when 50 mg ascorbic acid was added to infant cereal meal containing 5 mg iron as ferrous ammonium citrate.

Increased Absorption of Iron from Cereals with Addition of Ascorbic Acid with various Fortification Compounds

(Hurrell, 1998)

			% Iron absorption		
Study/Meal	**Iron compound**	**(mg)**	**Without ascorbic acid**	**With ascorbic acid**	**(mg)**
Derman et al. (1980)/ Infant cereal	**ferrous ammonium citrate**	**5**	**0.8**	**10.3**	**50**
	ferrous sulphate	**6.9**	**1.0**	**3.7**	**24**
Forbes et al. (1989)/ Farina with milk	**ferric orthophosphate**	**3**	**0.8**	**3.3**	**100**
	ferrous sulphate	**3**	**4.5**	**15.4**	**100**
	electrolytic iron	**3**	**3.4**	**8.0**	**100**

Figure 3f

Working with 3 different iron compounds, an INACG study by Forbes et al. (1989), demonstrated significant increases in absorption from a meal of farina and milk containing 3 mg iron. After the addition of 100 mg ascorbic acid, absorption of ferric orthophosphate rose from 0.8% to 3.3%, ferrous sulphate from 4.5% to 15.4% and electrolytic iron from 3.4 to 8%. These increases range from about two- to four-fold. (See Figure 3f).

Ascorbic acid is a very effective enhancer of iron absorption. It is thought to reduce iron from the ferric to the ferrous state and chelate the iron into an absorbable form. The disadvantage is that ascorbic acid is unstable under the stresses of heat and humidity found in food processing and in storage, especially in the climates of the developing world. This lack of stability means large overages must be added and that packaging needs to be relatively sophisticated. Consequently, ascorbic acid becomes a fairly expensive option to optimize absorption.

Optimizing Absorption by Phytic Acid Removal

Phytic acid, a powerful inhibitor of iron absorption present in cereal and legume products can be removed by various approaches. Most commonly the enzyme *phytase* is used to "dephytinize." In an unpublished study conducted with Cook (Kansas University Medical Center), iron absorption from a high phytate wheat soy cereal was compared under 4 conditions—no optimization, addition of 25 mg ascorbic acid, phytate removal with phytase, and both ascorbic acid addition and "de-phytinization." Iron absorption by 9 adult subjects was 1% with no optimization. There was no significant increase with the addition of 25 mg ascorbic acid. Absorption rose to 4% with phytate removal and 8% when both optimization techniques were used together. Less phytic acid and more vitamin C clearly will increase iron absorption.

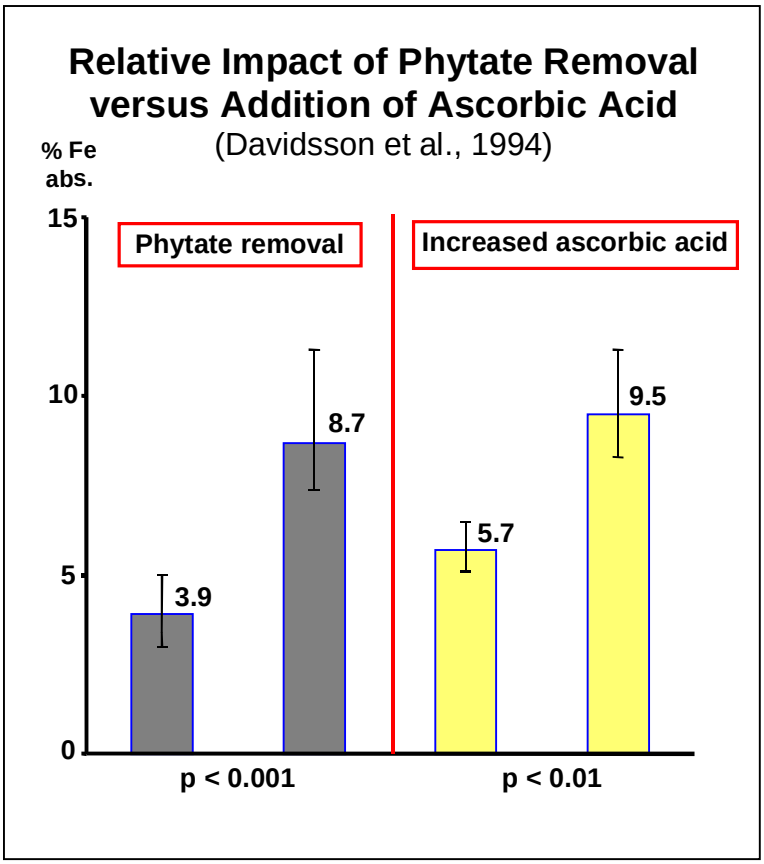


Figure 3g

The effect of phytic acid removal and ascorbic acid addition in a commercial soy formula product was studied by Davidsson et al (1994). Each liter of the product contained 20 mg iron from ferrous sulphate, 400 mg phytate and 100 mg ascorbic acid. The study design incorporated two optimization alternatives. One formulation degraded the phytate to 1.3 mg from 400 per liter while leaving the original level of ascorbic acid. The other alternative doubled the level of ascorbic acid to 220 mg per liter while leaving the phytate at the original level. Using stable isotopes, iron absorption was compared for each infant fed the same two meals. Absorption more than doubled, from 3.9% to 8.8%, with phytate removal and rose from 5.7% to 9.5% with increased vitamin C. Either optimization option was feasible for the manufacturer. (See Figure 3g).

When considering phytate removal, it is important to note that a substantial amount of the phytate, about 95%, must be removed before achieving a useful increase in iron absorption. It is not sufficient to remove half the phytate. In a study in which adults were fed a liquid formula meal of soy protein isolate in a medium of maltodextrin and corn oil, we found that when the phytic acid content was decreased in the soy protein isolate from 1000 mg to 400 mg per 100g, there was no improvement in iron absorption. However, when the phytate level was taken down below 200 mg per 100g, absorption began to increase and rose to about three-fold the original value when the phytic acid level reached level zero. (See Figure 3h).

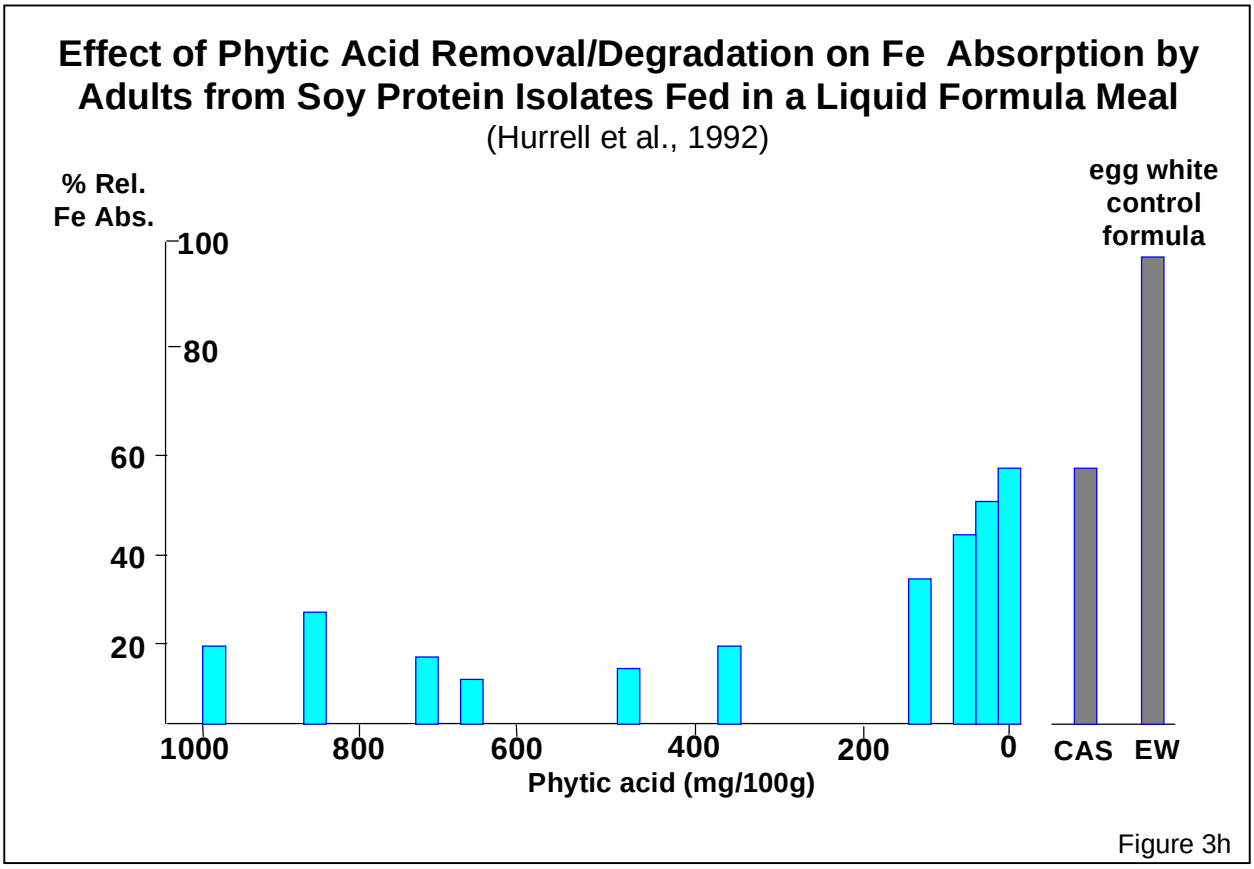


Figure 3h

Optimizing Absorption with Sodium EDTA

Sodium EDTA is a permitted additive in many countries, albeit in specified foods only. It is much more stable to processing and storage than vitamin C. When foods with added sodium EDTA are consumed, iron EDTA will be created from iron present in the common pool. This is because at pH-1, iron has the strongest binding constant to EDTA.

The impact of the addition of sodium EDTA alone has been shown in an unpublished radio iron absorption study (Hurrell, Reddy & Cook, 1992). In this study, adult subjects were fed two different infant cereals, one a high phytate soy based cereal, and the other a lower phytate wheat cereal. The meals included 50 g infant cereal with 300 ml

water, 5 mg iron as ferrous sulfate with varying concentrations of EDTA (at Fe:EDTA ratios of 1:0, 1:0.33, 1:0.67 and 1:1). Without the addition of sodium EDTA, the absorption of ferrous sulphate from the wheat cereal was only about 1%. With the addition of increasing concentrations of EDTA, absorption improved gradually up to a maximum of up to 6%. The same procedure with a higher phytate soy based product showed absorption rising from about 0.5% with no added EDTA to over 3% as the concentration of the sodium EDTA was increased. The study shows an increased absorption of ferrous sulfate with sodium EDTA of about six-fold, and demonstrated that sodium EDTA can be a useful alternative to ascorbic acid for enhancing iron absorption (Hurrell, R.F., Reddy M. and Cook, J.D., unpublished).

Recommendations

It is clear that absorption of even highly absorbable iron compounds may be unacceptably low from high phytate containing foods, which contain no ascorbic acid or other enhancers. After optimizing the iron compound and obtaining the maximum level and bioavailability with no organoleptic problems, absorption can still be improved via a number of methods.

The best way to optimize absorption from iron compounds depends on the facilities available. In industrialized countries, adding ascorbic acid or removing the phytate is usually the most effective approach. In developing countries, after optimizing the iron compound, the use of sodium EDTA as an enhancer may provide a useful alternative.

Sodium EDTA is more stable than ascorbic acid and is more realistic considering the less sophisticated packaging and storage found in developing countries. Sodium EDTA itself may also be used to enhance iron absorption.

Finally, in many developing countries, there are traditional processes which can activate the native phytates present in cereals and legumes. The phytates then degrade and lower levels of phytic acid. Soaking, germination and fermentation will degrade phytic acid. Fermentation is the most effective since the acid pH generated favors phytase action. However it should be stressed that iron absorption is only improved after phytic acid has been more or less completely degraded.

References

Fox, T.E., Eagles, J., Fairweather-Tait, S.J. (1998). Bioavailability of iron glycine as a fortificant in foods. American Journal of Clinical Nutrition 67, 664-668.

Derman, D.P., Bothwell, T.H., MacPhail, A.P., Torrance, J.D., Bezwoda, W.R., Charlton, R.W. &. Mayet, F.G.H. (1980). Importance of ascorbic acid in the absorption of iron from infant foods. Scan. J. Haematol. 45, 193-201.

Forbes, A.L., Adams, C.E., Arnaud, M.J., Chichester, C.O., Cook, J.D., Harrison, B.N., Hurrell, R.F., Kahn, J.G., Morris, E.R., Tanner, J.T. & Whittaker, P. (1989). Comparison of in vitro, animal and clinical determinations of iron bioavailability: International Nutritional

Anemia Consultative Group Task Force report on iron bioavailability. Am. J. Clin. Nutr. 49, 225-38.

Davidsson, L., Galan, P., Kastenmayer, P., Cherouvrier, F., Juillerat, M.A., Hercberg, S. & Hurrell R.F. (1994). Iron absorption in infants: The influence of phytic acid and ascorbic acid in formulas based on soy isolate. Pediatr. Res. 36, 816-822.

Hurrell, R.F., Juillerat, M.A., Reddy, M.B., Lynch, S.R., Dassenko, S.A. & Cook, J.D. (1992). Soy protein, phytate and iron absorption in man. Am. J. Clin. Nutr. 56, 573-578.

Iron Overload In Perspective

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Due to a misunderstanding of the main causes of iron overload, implementation of cost effective public health programs to reduce the significant burden of iron deficiency has been hindered in some countries. This is especially true with regard to iron fortification of staple foods.

Why the Concern About Iron Overload?

It is known that "free iron" (Fe^{3+} and Fe^{2+}) is a catalyst in redox reactions. In the human body such reactions result in the creation of free radicals (e.g. hydroxyl radicals) that can cause cell damage and death. Fortunately, natural mechanisms protect the body against such damage. Under normal conditions iron does not circulate freely in the body, but is bound by certain molecules such as transferrin, albumin and ferritin. The second line of defense against damaging "free iron" includes antioxidant compounds such as vitamin E or glutathione peroxidase, which scavenge the small amounts of free iron that may not be captured by the binding molecules.

Risk Factors for Iron Overload in the United States

The Center for Disease Control (CDC) considers the three major causes of iron overload in the United States as the result of non-nutritional factors:

a. One well-known cause of iron overload is acute childhood iron poisoning due to ingestion of large doses of iron supplements by unsupervised young children. When a child consumes a large number of iron tablets at one time, the body's protective mechanisms are overwhelmed. High doses, in the range of 200-250 mg per kilogram of body weight, can be fatal. In fact, this is the most common form of death due to childhood poisoning in the U.S. The solution to iron overload in this case does not include nutritional interventions, but rather accidental poisoning prevention. Prescription of iron supplements should include information and education for parents to prevent such accidents from occurring.

b. Certain health conditions, such as thalassemia major, which require repeated and regular blood transfusions present another important risk factor for iron overload. Each pint of transfused blood contains high amounts of iron, all of which enter the circulatory system directly and thus, lead to iron overload. Most physicians who treat such patients recognize the risk of iron overload and undertake the appropriate management—usually treatment with chelating agents. Thus, iron overload in individuals with hemoglobinopathies is not due to dietary factors but rather is the result of needed medical care.

c. The final but most common cause of iron overload in the U.S. is hemochromatosis—a condition where iron is absorbed at abnormally high rates. This is a genetic disorder that affects 1 in 300 persons—1 in 10 are gene carriers. Harmful levels of excess iron accumulate in the body over many years. Because of the "silent nature" of the disorder, clinical symptoms usually develop before the affected individual is identified unless specifically tested for the condition. Women of childbearing age are generally protected longer than adult men because of natural excretion of body iron stores through menstrual blood loss. Affected infants and young children have iron requirements that are similar to unaffected children in order to support their normal growth and mental development.

   Regardless of the various groups' relative risk of developing health complications as a result of the disorder, it should be recognized that *hemochromatosis cannot be prevented and may be only partially managed through dietary restrictions*. Iron is naturally present in many basic foods and, regardless of whether affected individuals consume fortified or non-fortified foods, they will accumulate high levels of iron in their bodies over time. Currently, the CDC makes no dietary recommendations for the management of hemochromatosis, except for advising against the use of iron supplements.

   The only way to protect individuals with hemocromatosis from the damage of iron overload is through early identification and timely therapy to reduce their iron stores—usually by phlebotomy. For individuals who do not know that they have hemochromatosis or are not receiving the appropriate treatment, even a normal diet will contain dangerous amounts of iron. In some situations, mainly in Western counties, there may be reason for concern about too much meat in the diet. Meat not only provides a large dose of iron, but the iron is also well absorbed—at a much higher rate than fortificant iron compounds. However, in developing country settings where access to animal foods is limited due to high cost, the role of meat as a dietary iron source is negligible.

Public Health vs. Clinical Perspectives

When making general recommendations to improve the health and nutrition status of populations, one has to consider the overall risks and benefits of programs and interventions. In developing countries, the public health burden of iron deficiency is far greater than that of iron overload (in many cases, more than 50% of young children and women suffer from iron deficiency anemia). This is not to say that the health problems associated with excess iron should be ignored. However, it is important to keep in mind that iron overload is primarily a condition that requires clinical management, and limiting the dietary iron intake of the whole population will not prevent the harmful effects of iron overload in the small proportion of people affected. Thus, con-

cerns about iron overload should not obstruct the implementation of much needed public health measures, such as iron fortification of staple foods, to reduce or eliminate iron deficiency.

Regulatory Status of Iron EDTA in the United States

John Vanderveen
USFDA

History of GRAS in the United States

Since the late 1930s, several iron sources have been used for fortifying foods in the United States. In the early 1940s, during the Second World War, standards of identity for enriched flour were established. Although the levels of fortification for the individual nutrients have increased, the basic requirements of these standards are still in place today. Fundamental to these standards is the concept that the added nutrients are in a safe form, i.e., that the levels of addition are adequate to meet the needs of the target population but not at levels that would cause harm.

The 1958 Food Additives Amendment to the Food, Drug, and Cosmetic Act (FD&C Act) allowed that if qualified experts deemed the use of compounds such as added nutrients, safe or Generally Recognized as Safe (GRAS) on the basis of common use in food prior to 1958, then the compounds would not require approval as food additives. The use of an ingredient can also be GRAS based on scientific procedures, but the GRAS status of most substances was based on common use in food prior to 1958. Additionally, any use of a food ingredient that had been explicitly approved by the Food and Drug Administration or the U. S. Department of Agriculture under appropriate laws, was considered to be prior sanctioned (by what may be considered a grandfather clause) and exempt from the need for new approval.

Many of these compounds with prior sanction or GRAS status under the 1958 Amendment to the FD&C Act had never been subjected to modern safety assessment. A few years later during the early 1970s, a Special Committee on GRAS Substances (SCOGS) evaluated the safety of each of the compounds that were GRAS by virtue of history. Based on reports from the SCOGS Committee, the FDA, through the process of public rulemaking, affirmed the GRAS status of many of the compounds that were added to food. Most, but not all, of the compounds which are used as nutrient sources have undergone that process. Those that were in common use prior to 1958 without safety problems and which have *not* gone through the affirmation process are still considered GRAS in the U.S. but are simply not affirmed.

New compounds that are found useful as fortificants can be determined to be GRAS by a sponsor if its safe use is generally recognized by experts. Alternatively, the sponsor can petition the FDA to approve the substance as a food additive. Under the U.S. system, any company can pursue a "self-determination of GRAS" if they are absolutely confident that there is consensus among food safety experts that there is no safety problem. If a sponsor has determined a substance to be GRAS, the Agency has proposed not to undertake efforts to affirm its GRAS status (because of resource con-

straints). However, if the sponsor was accurate in its assessment of GRAS status, the Agency would not challenge the sponsor's determination. By filing a food additive petition, a sponsor can secure a safety assessment for the new fortificant by the FDA.

Why Iron EDTA is not listed as GRAS in the United States

Iron EDTA has not been affirmed as GRAS in the United States for several reasons. First, it is not GRAS by virtue of its history of use since iron EDTA was not used commonly in food prior to 1958. Second, there appeared to be a high total use of EDTA in the U.S. food supply. EDTA is allowed for use in processing a variety of foods such as canned goods. The appearance of high levels of consumption for EDTA discouraged development of additional uses. According to earlier assessments of consumer exposure to EDTA in foods by FDA, the United States had reached recommended safe levels for total EDTA use as established by WHO/FAO Joint Expert Committee on Food Additives and Contaminants (JECFA). A third factor is simply that the FDA has never received a petition from a sponsor requesting the approval of iron EDTA, or even sodium EDTA and iron. There was some discussion but not an official GRAS affirmation request when the Agency was still accepting such requests.

Current Developments

On April 17, 1997 FDA proposed a new system for notifying FDA of self-determinations of food ingredients as GRAS. The Agency encouraged companies to notify FDA of their determinations and to eliminate the old program under which they "requested affirmation" of their determination. Under this proposed approach, a company can present its own assessment that a compound is GRAS and simply state that they were notifying the FDA. This gives the agency an opportunity to disagree, if errors are found in the company's research. To date the FDA has received several notices under this process for other substances.

In addition to this much-simplified process for claiming GRAS status, there has been a major change in FDA's assessment of EDTA use in this country. The FDA has reassessed consumer exposure to EDTA and found that there is room under the JECFA safe thresholds for use of EDTA. All that is needed is an expressed desire on the part of industry to use it.

The Future of EDTA in the U.S.

Some believe that high cost, up to six times the cost of ferrous sulphate, is a barrier to more widespread use of EDTA. However, this figure is based on the fact that industry is geared up for ferrous sulphate and other iron forms, not EDTA in particular. There are no efficiencies of scale to bring down the cost of EDTA. If indeed there was an opportunity to sell iron EDTA at the quantities of ferrous sulphate and other more commonly used forms of iron, then it would stand to reason that the price would likely come down.

In another recent development, the International Nutritional Anemia Consultative Group (INACG) has sponsored development of a toxicological monograph for sodium iron EDTA and submitted it to JECFA for approval. After review, JECFA has requested additional information regarding two issues. First, is the assurance that the site disposition of iron from sodium iron EDTA is not different than that of other iron compounds used for fortification. This is a traditional question that is asked during a toxicological evaluation. Second, is a determination of whether long-term use has any particular unique features compared to other forms of iron administration. This latter question involves a broad assessment of sodium iron EDTA in laboratory animals to determine how well the animals grow and other factors. INACG is currently gathering data on these issues and will undertake appropriate animal studies to answer these questions.

Conclusion

There has been much discussion about the superior bioavailability of sodium iron EDTA and iron and EDTA under certain conditions. To some degree, these compounds are effective in achieving the same amount of iron absorbed with less total exposure to iron (i.e., less total iron in the diet). Nevertheless, there is significant pressure from some hematologists in this country to constantly look at fortification in the U.S. food supply. They maintain that levels of fortification are already too high and that we should consider lowering them. On the other hand, there are many experts who believe that our level of fortification in the U.S. is about right. We at the FDA agree, although we will continue to monitor data (from the National Health and Nutrition Examination Surveys (NHANES) and other surveys—particularly serum ferritin levels and other indicators of iron status).

If similar effectiveness in preventing iron deficiency with smaller amounts of more highly biologically available compounds can be achieved, this should be considered. For those people in the U.S. who are still not achieving healthy iron status, these compounds may actually prevent deficiency. Finally, there is always interest in the potential of greater stability in formulated products. I would predict that sometime in the near future, iron EDTA will be approved for use in this country and throughout the Western world and then the issue will not be regulatory but rather cost and functionality. We are aware that manufactures would like to initiate the use of sodium iron EDTA in the very near future because they believe that its use will improve the stability of their products and at the same time improve iron absorption. Provided that there is no hidden risk, these are very worthy goals.

DISCUSSION

Peter Ranum
Moderator

"Is there sufficient information to recommend a simple and uniform procedure for addition of an iron compound?"

Q *There are large flour fortification programs gaining momentum in several parts of the world where high extraction and high phytate flours are common. Is there sufficient information on this issue to recommend a simple and uniform procedure for addition of iron compound? Perhaps there may be enhancers such as EDTA or ascorbic acid, that will be stable, bioavailable and organoleptically acceptable in conditions found in developing countries?*

A There is a lot of information showing that sodium iron EDTA does overcome the inhibitory effects of phytic acid in high extraction flours. Moreover, organoleptic studies with iron EDTA in wheat flour have reported no pentane buildup after 6 months at 37°C indicating that it is quite stable. On the other hand, if sodium EDTA and ferrous sulfate are put in the same wheat flour, there are organoleptic problems. So in wheat flour the recommendation for higher phytate flours should be to add fortification iron as sodium iron EDTA and not ferrous sulfate plus EDTA. However, even with sodium iron EDTA, there is a need to do more thorough organoleptic studies.

Another possible approach for high extraction wheat flour is to add encapsulated ferrous sulfate that would protect the compound and help prevent oxidation of the flour fat during storage. It probably does not matter if the encapsulating coating comes off after the flour has been used in baking because at that point there are no color changes that take place in the flour.

The general principle is that when an iron compound is added to a food such as wheat flour that contains absorption inhibitors, there will be no nutritional benefit unless something is added to enhance the bioavailability of the iron compound and/or protect it from the inhibitors in the flour or from inhibitors in the entire meal. It is not sufficient to just add iron—one must protect it and enhance absorption.

"Venezuela's fortification program has proved to be quite successful—even though no absorption enhancers were added."

Q *Work has been done on Egyptian baladi bread using sodium EDTA with and without ferrous sulfate. The bioavailability of the ferrous sulfate was improved about three-fold. Since baladi bread is baked at a high baking temperature, this shows that EDTA is stable at this very high temperature. Certainly, vitamin C would not survive this environment. In order to avoid the organoleptic problems emerging from the mix of ferrous sulfate with sodium EDTA, might elemental iron be used with the sodium EDTA instead?*

A In terms of avoiding this interaction, ferrous fumarate would be superior to elemental iron. In fact, ferrous fumarate is used in Venezuela's fortification program which has proved to be quite successful—even though no absorption enhancers were added under the Venezuelan fortification profile.

Vitamin A was added in Venezuela and studies done by Layrisse and lead some people to believe that vitamin A can act as an enhancer of iron absorption. However, we have done some studies and have not been able to show that vitamin A enhances iron absorption. Nevertheless, ferrous fumarate, is quite a good iron compound to add to some cereal flours.

"Fermentation of dough would be a good way to reduce phytic acid levels"

Q *In some Middle Eastern countries, bread dough goes through a short period of fermentation prior to baking. Should we promote this process as a strategy to decrease phytates and increase bioavailability? Sometimes the bread dough may not be fermented long enough. However, if a longer period of fermentation would increase bioavailability, people can be encouraged to ferment for a longer period of time.*

A Fermentation of dough would be a good way to reduce phytic acid levels. Essentially, fermentation works by taking the pH level down. Since the enzymes like phytase are much more active at pH5 than pH7, fermentation enhances phytase activity and speeds the degradation of the phytic acid. It is interesting that wheat itself contains the enzymes that can act to degrade phytic acid. We have done some studies just holding the wheat flour, not even fermenting it. Given enough time, this actually does degrade all the phytic acid in wheat flour—simply by letting it stand.

Research is needed to determine whether adding phytase as an additional enzyme to wheat flour in order to degrade phytic acid, is a feasible strategy to increase bioavailability of fortification iron.

"The level of meat consumption... can predict the level of IDA. However, infants remain at-risk."

Q *In Mexico, Procter & Gamble originally used ferrous pyrophosphate in its Choco-milk, a powdered milk enhancer product, and then switched to ferrous fumarate. During clinical efficacy studies in Mexican schools, teachers would tell us that even though the trials were double blind they could identify which students were getting the fortified versus the non-fortified product simply because they could see an increase in attention and even excess energy. In Latin America, since there are many different staple foods and food habits, is there a parallel difference in the rates of IDA? For example, in some countries like Argentina, consumption of meat is quite common while in other countries it is relatively rare. Do these kinds of differences impact prevalence rates?*

A Meat consumption has a strong predictive value on IDA rates. Argentina has one of the highest levels of red meat consumption in the world and, for the adult population, the rate of IDA is quite low. Generally, by looking at the level of meat consumption, one can predict the level of IDA. However, the general level of meat consumption notwithstanding, infants remain at risk. This is because until the second year of life, when infant diets begin to change to include items in the general diet, the infant diet is milk based. Whether they are breastfed or receive a liquid or powdered formula, infants will continue to be at risk for IDA unless special provisions are made. For example, until 12-15 years ago the IDA rate for infants in Argentina was similar to other countries in the region—countries with only a fraction of Argentina's meat consumption. That was a very valuable data for public health strategists because it demonstrated that you cannot assume that infants are not at risk of IDA just because their diet is high in iron for the adults population. To protect infants, special approaches need to be developed. So although one can predict the general IDA situation by looking at the population-wide adult diet, infants are a more vulnerable group and interventions should be based on their special diet.

"We have long heard about an unidentified 'meat factor' that enhances absorption of iron"

Q *The presence of meat enhances absorption of iron. Not only is heme iron absorption much greater, but the presence of heme iron also increases absorption from less bioavailable iron in vegetable and grain products found in the non heme pool. We have long heard about an unidentified "meat factor" that enhances absorption of iron—independent of the heme iron itself. Is there such a factor and can we make use if in fortification?*

A Most of the work on the "meat factor" subject has been done in Venezuela where studies have shown several times that meat or muscle tissue enhances iron absorption. These same studies demonstrated convincingly that the increased absorption is due to the cystine containing peptides in that meat. To isolate this "meat factor" for use as an independent absorption enhancer by the food industry involves a lot of work—identifying those peptides, isolating them, and making them an acceptable food additive. No one is pursuing this research at the present time, but it is something that might be done.

"Rice has presented challenges for a long time. At this point there is no fortified rice with good iron bioavailability."

Q *Rice has been viewed as a potential vehicle for iron fortification for many years. Like other staples including flour, rice also contains phytates. However, unlike wheat and corn flours, in most developing countries, rice is washed before it is cooked. Given these obstacles, is there a recommended technology for the fortification of rice with iron?*

A Rice has presented challenges for a long time. At this point there is no fortified rice with good iron bioavailability. In the United States, where some rice is fortified, the iron compound of choice is ferrous orthophosphate which is not very bioavailable or soluble but is very acceptable from a organoleptic point of view. We have tried to get a more bioavailable rice. We have tried coating. However, this is a complicated problem. The coating may be too thin and wash off. On the other hand, the coating may work too well and consequently does not come off in the gut or become available for absorption. The alternative approach is simulated rice granules. That involves having the right dies to cut a kernel that looks like the raw rice and simulating a rice that cooks the same as natural rice. Normally the formula for mixing the simulated kernels with natural rice is 1:100-200 depending on the iron level.

In Indonesia, the Micronutrient Initiative has done a small-scale trial of rice fortification using the simulated kernel approach. A technology has been donated by the Bon Dente Company. This technology provides a vehicle for multiple micronutrients in rice—including iron as well as vitamin A. Basically, the Bon Dente technology uses inexpensive broken rice kernels which are ground into a fine powder mixture. Micronutrients are added and finally the kernel is reconstituted. After this "premix" of simulated rice kernels is produced, it is mixed with natural rice at a predetermined ratio. From a purely technological point of view this is a very feasible approach to getting micronutrients delivered via the rice distribution system.

"If we can make progress with the decentralized producers of salt we should be able to do it for rice producers as well."

A The real challenge in rice fortification is not the technology but the commercial infrastructure. In many Asian countries where rice is a staple, production and distribution is very decentralized. This presents several obstacles. First, there are difficulties in getting the simulated rice kernels or "premix" to these far flung and relatively small scale producers in a cost effective manner. Second, there are barriers to motivating these producers to use the micronutrient mix in their processing and subsequently getting consumers to buy it. Third, there is the issue of safety and quality assurance in this decentralized setting. In summary, the technology is available but the issue in one of cost-effectively scaling-up to a commercial or national level.

In the very successful campaign to iodize the world's salt, this issue of small scale decentralized processing was brought up as a barrier. However, the barriers were overcome and salt iodization has become a successful campaign worldwide. If we can make progress with the decentralized producers of salt, we should be able to do it for rice producers as well. The barriers are real. However, considering the large populations relying on rice as a staple food and the huge potential to improve iron status, we need to find ways to capitalize on rice fortification so that countries can actually use it.

"Even though the per person cost or the rise in retail cost is quite low, some middle-men or food processors take advantage of this 'improved product' to inflate the cost"

Q *Even though the per person cost or the rise in retail cost is quite low, some middle-men or food processors take advantage of this "improved product" to inflate the cost far beyond the actual incremental cost of fortification. Ultimately, when you raise the price the product becomes too expensive for some of the low-income populations who are most at risk. How do you work to prevent that this kind of mark-up?*

A The pressures to inflate the cost of fortification are real. For example, in Indonesia when noodle manufacturers were approached, they agreed that a premix could be added at the point of noodle production at an added cost of about 1 rupiah. However, they insisted that their minimum price increment at the retail level had to be 25 rupiah. In the commodity market for staple foods, however, the situation is very different. The profit margins are thinner.

The cost issue is always the most sensitive one. In Indonesia, the government agreed to go forward with fortification for several reasons. The government subsidizes the cost of wheat flour about 30-45%, depending on the currency fluctuation. Therefore, for all practical purposes the incremental cost of fortification will be borne by the government. So even though the retail price increment due to fortification is quite small, the government had to look at a total cost of $4-5 million. However, given the small per capita costs and the large potential benefits of improving iron status, the government agreed this total cost was reasonable—even for a government under severe economic stress as is the case in Indonesia today. Moreover, since flour subsidies will be withdrawn in the near future as part of the overall economic reform in Indonesia, the government understood that this added $4-5 million annual burden was not a long-term drain on the public treasury and would eventually be passed on to the consumer.

Governments get involved in subsidizing flour in order to keep the prices low. Since the government is bearing the initial costs with the public interest in mind, this inflated mark-up problem will not arise in Indonesia. Moreover, the flour mills in Indonesia are coming under severe pricing and other competitive pressures. Therefore, in this environment, we do not believe they will be able to inflate the cost of fortification beyond the actual cost of premix. So we anticipate the incremental cost of flour will be proportional to the cost of fortification—mainly the cost of premix.

In countries such as Indonesia where all the wheat is imported, the price of flour largely depends on the international price of wheat. This fluctuates widely with each crop. This usual variation in the price of wheat completely washes out any cost increase caused by fortification of flour. The consumer will eventually pay for it, should be expected to pay for it, and can afford it. However, getting over that initial cost hurdle that can be quite difficult. On the other hand, the fortificant cost, the major cost of fortification, also fluctuates. For most developing countries, the fortificant is usually imported and the cost is based on the U.S. dollar. Consequently, the cost of the fortificant is very vulnerable to swings in the value of the local currency. Earlier this year in Indonesia, the cost of fortificant doubled in just a few days because of the fall in the rupiah.

"There is no evidence that fortification iron at food levels will produce any side effects"

Q *In certain subjects supplemental iron causes constipation. What form of iron is least conducive to this problem and what level would be the most effective in preventing constipation?*

A Side effects with iron supplements are significant. There have been no well controlled studies on this subject, so we can only speculate based on incomplete data. However, there is some evidence that the only way to reduce upper gastrointestinal side effects such as epigastric pain and heartburn, is to reduce the amount of soluble iron in the stomach. Theoretically, prescribing an insoluble iron salt would solve this side effect. However, an insoluble salt is not absorbed and provides no nutritional benefit. It seems possible that these side effects could be reduced by using a form of iron that is gradually delivered to the stomach. In fact, there have been attempts to design a capsule that does not dissolve immediately but sits in the stomach and gradually releases the iron. Through this "timed release", the concentration at any one time is fairly low and therefore the likelihood of the side effects decreased. The other option is to reduce the dose. In western countries, prescribed doses are often unnecessarily high. Often people forget to take supplements in the fasting state or take it with vitamin C which may increase side effects. The bottom line is that no good solution to the constipation problem exists. But it is important to keep in mind that the level of iron found in fortified food is much lower that the level in supplements. There is no evidence that fortification iron at food levels will produce any of these side effects.

"Based on the best available epidemiological data, in the United States there are no dramatic variations in IDA among socio-economic groups"

Q *In the United States IDA still tends to cause problems in a number of geographic areas and among specific populations of pregnant women, adolescents and young children. Are there cost effective opportunities for making fortified products available to people at risk of IDA in the United States?*

A Based on the best available epidemiological data, there are no dramatic variations in IDA among socio-economic groups in the United States. For example, there is no difference in IDA rates in children from lower versus higher income families The reason for this is a special food supplementation program for women, infants and children (WIC). This program essentially guarantees that all non-breastfeeding children get iron fortified formula. WIC has virtually eliminated IDA among low-income families in the U.S.

For pregnant women, the primary risk factor is not dietary. The major risk factor for the 30-40% of women who have insufficient iron stores at the time of pregnancy is relatively greater menstrual blood loss during the times prior to pregnancy. That is a risk factor not dependent on income or socioeconomic status. Therefore, the best way to deal with this problem is a traditional clinical approach not a dietary one. CDC recommends screening women for iron stores and hemoglobin levels to identify those at high risk. After screening supplementation is recommended for those who show evidence of IDA—either before pregnancy or during pregnancy.

It would be very problematic to develop a population-wide program of fortification just to eliminate the risk in a small percentage of women. Given the overall iron content and bioavailability from the general diet in the United States, I think the benefit to be derived from a national staple food fortification program is marginal. But this country has been doing it for 50 years. It is a tradition. There have been no problems over these 50 years and its unlikely anyone will raise objection to continuing fortification.

Even though the United States has been fortifying many foods with iron for a long time and iron deficiency rates are quite low, IDA remains a concern among special populations—pregnant women and young children. This indicates that fortification, by itself, will not solve the problem. Based on USDA studies only 75% of the female population in the U.S. consume the recommended amount of iron in their diet. So even though fortification does help reduce the magnitude of the problem, other strategies are needed. Identification of risk groups and reaching them with supplements is one approach. Also, as long as people

make food choices, nutrition education will be important. These strategies need to be considered and refined on a continual basis, along with fortification.

Unlike other therapies for IDA, fortification is a very long-term proposition. The low rate of iron deficiency we have achieved in the United States has been a long time in the making. Fortification is not something that is going to change iron status very quickly. It is going to prevent iron deficiency and slowly correct iron deficiency anemia. Fortification will add 0.5 to 1 mg iron consumption a day. Often the deficit is perhaps half a gram or more. Fortification cannot overcome that gap overnight. It is a long-term solution, taking perhaps several years to bring the population into a reasonably good iron status.