The importance and limitations of food fortification for the management of nutritional anemias[1]

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[1] From A2Z/The USAID Micronutrient and Child Blindness Project, Washington DC.

INTRODUCTION

The customary diet of populations in developing countries (1) and population subgroups in developed countries (2) does not have the adequate micronutrient balance to satisfy the requirement of one or more nutrients. This occurs due to economic[2], cultural[3] or physiological[4] reasons, making the addition of micronutrients an appropriate intervention. Two approaches can be used for this purpose: dietary supplementation and food fortification.

A dietary supplement is a product which requires a voluntary and educated decision for consumption. Supplements are highly dense in vitamins and minerals to provide large amounts of nutrients in one or few doses. The formulation of dietary supplements can be tailored to the requirements of specific population groups. They may also deliver adequate amounts of micronutrients and the interactions of micronutrients and absorption inhibitors—mainly for iron, zinc, copper, and calcium—can be diminished (3). Supplementation programs often have a disadvantage of low population coverage and acceptance.

A fortified food can be defined as an edible product (staple food, processed food, condiment, or product for special groups) manufactured by the food industry with a nutritional composition that is enhanced by the addition of vitamins and minerals. The WHO Guidelines for food fortification (4) distinguishes three approaches to food fortification: mass, targeted, and market-driven. Mass fortification refers to the addition of micronutrients to edible products that are consumed regularly by the general public, such as cereals, oils and vegetable fats, milk, and condiments. Targeted fortification refers to the fortification of foods designed for specific population subgroups, such as complementary weaning foods for infants, foods for institutional programs aimed at schoolchildren or preschoolers, and foods used under emergency situations. Market-driven fortification refers to a situation in which a food manufacturer takes the initiative to add one or more micronutrients to processed foods in order to increase sales and profits.

Adding micronutrients in each type of fortification approach requires different guidelines. In any case, the objective is to provide the intended benefit for the target population while avoiding potential risks associated with excessive micronutrient intake to individuals who consume the fortified products in large amounts. That means the micronutrient content is limited to prevent individuals from surpassing the Tolerable Upper Intake Level (UL)[5]. Other restrictions result from negative interactions with the food matrices and the need to minimize the additional cost (4,6). Because of this, the supply of some micronutrients, mainly through mass fortification, may be insufficient, especially for individuals in the most at risk groups. The advantage of mass fortification, however, is that population coverage is large.

Targeted fortification has an intermediate position between dietary supplementation and mass fortification. While it can deliver high

[2] Little access to good quality and nutritious foods, e.g.

[3] Strict vegetarianism or diet largely based on starchy or refined foods, e.g.

[4] Low gastric capacity in small children, larger nutritional requirements during pregnancy or lactation, or reduced intestinal absorption in the elderly, e.g.

[5] The Tolerable Upper Intake Level (UL) is the highest average daily nutrient intake level unlikely to pose risk of adverse effects to almost all apparently healthy individuals in an age- and sex-specific group (5).

amounts of micronutrients, the population coverage is restricted and some undesirable interactions between micronutrients and other diet ingredients may still occur. With targeted fortification, the limitations due to sensorial changes in the food matrix are less restrictive than with mass fortification.

The importance of market-driven fortification in developing countries is still uncertain because of the generally low accessibility of these foods to the poor and to rural groups. Another disadvantage is the potential risk of providing excessive intakes to some consumers. Thus, the balance of the micronutrient content to the energy density in the food is increasingly being recommended as the guideline to determine the micronutrient amounts for this type of fortification (2, 4).

Lastly, it is important to recognize the concept of household fortification. This term identifies the consumption of dietary supplements (usually in powder forms) mixed with foods during meals. In this case, the conditions that are established are similar to those of targeted fortification (i.e., probably high micronutrient intake), but limited population coverage, still with possible negative interactions between the minerals and the ingredients of the diet.

This chapter discusses food fortification to address nutritional anemia. Two population groups are especially vulnerable to anemia: children younger than 24 months of age and women of reproductive age. The former group should receive special attention and products, such as complementary foods (targeted fortification) and age specific dietary supplements. Therefore, fortification for young children is not included here. This chapter focuses on the use of food fortification to manage nutritional anemia in women of reproductive age, although it also describes a few studies that assessed biological impact in school-age children.

JUSTIFYING AND DESIGNING MASS FORTIFICATION

Cost of correcting micronutrient deficiencies

Nutritional anemia is only one of the consequences of micronutrient deficiencies, but is usually the most difficult to overcome. Nutritional anemias have been usually associated with deficiency of iron. While this may be the case, the status of vitamins A, B_2, B_6, B_{12}, and folate must also be adequate for the synthesis of hemoglobin (7). Because hemoglobin is carried by red blood cells, many other nutrients that ensure cell replication, growth and maintenance are also needed, including those participating in energy metabolism (vitamins B_1, B_2, and niacin), in protein and nucleic acid synthesis (vitamins B_2, B_6, B_{12}, niacin, and folate), in genetic modulation (vitamins A and D, and iodine), and in the protection against oxidation (vitamins C and E, magnesium, selenium, and zinc) (8,9). A sufficient supply of essential amino acids, fatty acids, and metabolic energy is also necessary. Supplying additional iron would reduce anemia only if iron is very deficient and only up to the point where another factor becomes rate limiting. In the case of poor societies, other factors – both nutritional and environmental – could be present (10). Therefore, management of nutritional anemia requires good general nutrition conditions and the improvement of the status of many micronutrients, not just iron.

Table 19.1 lists the current cost to supply the estimated average requirement (EAR)[6] of nutrients

[6] Estimated average requirement (EAR) is the average (median) daily nutrient intake level estimated to meet the needs of half the healthy individuals in a particular age and gender group. These are the dietary parameters recommended to assess and plan population-based interventions (5).

Table 19.1: Calculated costs to provide one estimated average requirement (EAR) to women of reproductive age through food fortification.

Micronutrient	Fortificant	Micronutrient in fortificant (proportion)	Fortificant price ($/kg)[1]	Micronutrient loss before consumption (%)	EAR[2] (mg/day)	Cost to supply EAR ($/year)[3]
Vitamin B_1	Thiamin mononitrate	0.81	25.00	30	0.9	0.013
Vitamin B_2	Riboflavin	1.00	38.00	15	0.9	0.014
Niacin	Niacinamide	0.99	10.00	10	11	0.045
Vitamin B_6	Pyridoxine	0.82	31.00	15	1.1	0.017
Vitamin B_{12}	Vitamin B_{12} 0.1 % WS	0.001	42.00	15	0.002	0.035
Folate	Folic acid	1.00	90.00	30	0.188	0.008
Vitamin A	Retinyl palmitate (oil)	0.51	70.00	30	0.357	0.023
	Retinyl palmitate (dry)	0.075	40.00	30	0.357	0.090
Iron	NaFeEDTA	0.13	6.50	0	9.4–14.1[4]	0.172–0.257
	Ferrous bisglycinate	0.20	25.00	0	9.4–14.1	0.429–0.643
	Ferrous fumarate	0.32	7.05	0	14.1–28.2	0.113–0.227
	Ferrous sulfate (dry)	0.32	2.60	0	14.1–28.2	0.042–0.084
	Micronized ferric pyrophosphate	0.25	9.10	0	20.1–40.3	0.267–0.535
	Electrolytic iron	0.97	4.50	0	21.6–43.2	0.037–0.073
	Hydrogen reduced iron	0.96	3.25	0	28.2–56.4	0.035–0.070
	Encapsulated ferrous sulfate	0.16	13.00	0	14.1–28.2	0.418–0.836
Zinc	Zinc oxide	0.80	3.35	0	4.1–8.2	0.006–0.013
Iodine	Potassium iodate	0.59	20.00	15	0.107	0.002
Calcium	Calcium carbonate	0.40	2.70	0	833	2.105
Vitamin C	Ascorbic acid (fine powder)	1.00	11.20	60	37	0.242

to women of reproductive age through food fortification. Cost varies from the least expensive nutrient, iodine ($0.002 per year), to the most expensive, calcium ($2.105 per year). The higher cost of calcium is mainly due to the large amounts of the mineral needed. Costs of iron, vitamin C, and vitamin A follow after calcium. These costs are estimated also taking into consideration the expected micronutrient losses during production, distribution, storage, and food preparation. The costs are also adjusted to consider the estimated physiological biovailabilities. Iron costs range from $0.035 to $0.836 per year, depending on the iron compound and the diet characteristics. The cost of vitamin C is approximately $0.242 per year, and the cost of vitamin A can vary from $0.023 per year to $0.090 per year. The cost of combining all the other micronutrients listed in the table is lower than $0.150 per year.

Under typical conditions (excluding calcium and vitamin C[7]), it is estimated that a woman can receive her entire yearly requirement of micronutrients through food fortification activities with an annual investment of $0.35 to $1.00. The type of iron and vitamin A compounds determine the variation in costs. This investment would be lower if we consider that food fortification aims to cover the gaps between a person's nutritional needs and their usual diet. This means that food fortification could be the most favorable and cost-effective strategy among micronutrient interventions. However, as described below, many factors can hinder the potential use and efficacy of food fortification.

In mass fortification under formal industrial settings (large factories), approximately 80–90% of the cost corresponds to the purchase of micronutrient compounds (13, 14). Thus, the cost of the fortificants is a proxy estimation of the overall cost of mass fortification. Such a generalization is valid neither for small operations nor rice, which is fortified by using micronutrient coated or artificial kernels. In the latter case, 50–90% of the cost is associated with production of the fortified kernels.

With supplements, the cost of the micronutrients represents 10–40% of the overall cost. If one assumes that each supplement cost $0.02, and that a weekly delivery may require 50% higher doses than the daily scheme to compensate for lower absorption, then daily and weekly schemes would need annual investments to manufacture the product in the order of $7.30 and $2.00, respectively. The cost of the weekly scheme is attractive if it were biologically efficacious. Recent evidence suggests that this is indeed the case, at least for some micronutrients (15), which

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[7] Calcium because of the relatively large amounts needed, and vitamin C because the high loss during storage and during food preparation is usually not included in most mass-food fortification cases.

Table 19.1

[1] Vitamin information provided by DSM, the Netherlands; most mineral information by Paul Lohmann, Germany; NaFeEDTA by Akzo Nobel Chemicals, Singapore; and ferrous bisglycinate as in the market.

[2] All micronutrients, except iron, as specified in Allen (4). Folate expressed in Dietary Folate Equivalents (i.e., 1 mg folic acid=1.7 mg DFE), and EAR of vitamin B_{12} divided by two because of higher bioavailability of the synthetic form. Iron values for diets with 10% and 5% iron bioavailability were estimated from the Institute of Medicine of the USA (5), dividing the absorbed iron need (1.4 mg/day) by 0.10 and 0.05, respectively. EAR values for each iron compound are approximations based on their relative biovailabilities as compared with ferrous sulfate.

[3] Cost=(EAR x 365) x (fortificant price x (1 + (% loss/100)) / (micronutrient proportion x 10^6).

[4] First figure is an approximation for a diet whose general mineral bioavailability is intermediate (10% for dietary iron), the second figure corresponds to a diet of low mineral bioavailability (5% for dietary iron). EAR for electrolytic and hydrogen reduced irons are estimated as 65% and 50% as ferrous sulfate, respectively, following data of relative bioavailability (11). EAR for micronized ferric pyrophosphate was estimated as 70% that of ferrous sulfate (12).

justifies further attention to this strategy. Dietary supplementation requires a distribution system, while one is usually already operative in the case of mass fortification. Creating this new system may be a very expensive and challenging task. Therefore, the absence of cost due to distribution, rather than the cost of the fortificants, demarcates the main advantage of mass fortification over supplementation and the other fortification approaches.

Vehicle selection

The low cost of using mass fortification over supplementation or targeted fortification holds true only in industrial settings, where only few acceptable developed factories produce the foods. That means that the main criterion for mass fortification is that the fortification vehicle should be produced by formal and centralized industries. Otherwise, the economic advantages of this intervention might be significantly reduced or even lost. These advantages include the fast pace and low cost for implementation, the production following good manufacturing practices, the easy distribution and control of the micronutrient mixes, and the feasibility of the essential regulatory enforcement by the government. The above consideration is contrary to the common paradigm that a widely consumed food, regardless of the system of production and trade, such as staple cereals and salt, is a suitable fortification vehicle. In many instances, results of biological efficacy of fortification projects implemented in small operations, under strictly controlled and subsidized schemes, are used as evidence of the feasibility of this practice. The fact that biological impact depends on the quality and amount of the added micronutrients and not on the mechanism of delivery, and that operational success under controlled conditions does not predict program viability, is often overlooked. Hence, it is important to recognize that the social penetration of a mass fortification program is determined by the extent to which the centrally-produced foods are distributed, and by the amount of products that are accessible and affordable to the at risk population.

Table 19.2 presents some characteristics of ongoing mass fortification programs. Two of these characteristics are essential in predicting the feasibility of a mass fortification program: 1) high dilution factor of the fortificant (source of micronutrients) in the food; and 2) low cost expressed in relative terms to the price increase of the commodity. If these two conditions are met, the chance of introducing a mass fortification program improves and the risk of noncompliance is reduced. Except for fish/soy sauces fortified with NaFeEDTA, which show a dilution factor in the hundreds and not in the thousands, the other fortification examples included in the table fulfill the mentioned requirements.

Fish and soy sauce fortification is being introduced in Vietnam and China (16), respectively, but the establishment of real mass fortification programs has not as yet been demonstrated. It is possible that, in the absence of a very strong governmental pressure, this fortification effort may end as a “market-driven” fortification of a few brands, or end as targeted fortification sponsored by institutions outside of the food industry. The same restrictions may hinder the introduction of mass fortification of rice using micronutrient coated or artificial kernels; the dilution factor is 1:100 to 1:200 (17) and the raise in price is between 3 and 6%. A very small number of countries have rice mills in a position to produce rice under such conditions. The failure of fortification efforts with vitamin A of monosodium glutamate in the Philippines and Indonesia in the 1970s may provide an example of how real this threat is. The project, although biologically efficacious, collapsed a few months after initiation because of product discoloration in Indonesia, and because the price increase was too large to favor acceptance of the product by the consumers in the Philippines (18).

The maximum dilution factor possible in mass fortification depends on the physical weight and volume of the fortificants, their proportional

Table 19.2: Comparison of dilution factors, and costs of existing mass fortification programs.

Food	Micronutrients and average contents (mg/kg)	Grams of fortificant per 1000 kg or L	Dilution factor fortificant: food+fortificant	Fortificant cost ($/1000 kg or L)	Food price ($/kg or L)	Price increase due to fortification
Salt	Iodine (40)	75	1:13,333	1.36	0.20	0.7%
Oil	Vitamin A (20)	40	1:25,000	2.75	0.50	0.5%
Sugar	Vitamin A (15)	200	1:5,000	8.00	0.40	2.0%
Milk	Vitamin A (0.6), Vitamin D (0.01)	75	1:13,333	1.50	0.60	0.2%
	Folic acid (0.2)					
	Iron (bisglycinate) (10)					
	Zinc (7.0)					
Low extraction	Vitamin B_1 (6), Vitamin B_2 (5)	250	1:4,000	2.17	0.40	0.5%
wheat flour	Niacin (60), Folic acid (2)					
	Iron (ferrous fumarate) (45)					
Low extraction	Vitamin B_1 (6), Vitamin B_2 (5)	400	1:2,500	4.00	0.40	1.0%
wheat flour[1]	Niacin (60), Vitamin B_6 (6)					
	Vitamin B_{12} (0.01), Vitamin A (2)					
	Folic acid (2), Zinc (30)					
	Iron (ferrous fumarate) (45)					
Fish/soy sauce	Iron (NaFeEDTA) (500)	3,846	1:260	25.00	1.00	2.5%

[1] Some African countries have proposed using a formula like this, while Jordan and the Palestinian territories have already introduced the same micronutrients, but at around one half of the amounts shown here, because of the large consumption of wheat flour in those countries, and the use of ferrous sulfate as the iron source.

content of micronutrients, and the selected micronutrient content for the fortified food. For example, in the case of sugar fortification with vitamin A, the maximum possible dilution factor to produce fortified sugar with a content of 15 mg/kg, using an encapsulated compound of vitamin A that contains this nutrient at 7.5% (w/w, weight per weight), is 1:5,000 (i.e., 200 g of fortificant per 1,000 kg of fortified sugar). This means that one part of the compound containing vitamin A is present for each 5,000 parts of fortified sugar. However, this dilution factor may be too large to make a homogeneous product. Thus, the vitamin A compound is diluted first to 1:5, to reduce the dilution factor to 1:1,000 (i.e., 1 kg of fortificant premix per 1,000 kg of fortified sugar). Nevertheless, dilution factors lower than 1:1,000 may be very cumbersome for the staple industries to implement, because large volumes and weights are difficult to handle, store, distribute and dilute.

Design of the fortification formulation

Annex D of the WHO Guidelines on food fortification (4) describes a procedure to estimate the micronutrient content in mass fortification. In brief, the model is based on the determination of a Feasible Fortification Level (FFL). The FFL is the maximum content of micronutrient that can be added and still remain compatible with the food matrix; it increases the price of food within an acceptable value; and it provides the greatest number of at risk individuals with an adequate intake without causing an unacceptable risk of excessive intake in the population at large. A mass fortification program can be constituted by more than one food vehicle. Then, the FFL for each micronutrient and food should be estimated in cumulative sequence, starting with the food with the largest market penetration. An alternative approach is to make a combined analysis of all foods that are being considered as part of the program. In either case, the objective is to reduce the risk of excessive intakes for those individuals who consume these foods in large quantities and at the same time to provide as much micronutrients as possible to the population at risk. As a consequence, the maximum content of micronutrients in mass fortification is determined by those individuals who eat the food vehicles in the largest quantities (i.e., the upper 5–10%). This can result in a situation in which important portions of the population at nutritional risk may still not receive sufficient additional intakes to fulfill their nutritional gaps. Thus, complementary measures may still be needed. This circumstance affects mainly those micronutrients with UL values near to the EAR values, such as folic acid, vitamin A, iron, iodine and calcium. These nutrients coincidentally are among the micronutrients whose intake should be raised among poorer populations.

For nutrients without recognized UL values, the FFL may be higher than necessary to satisfy the nutritional gap of most of the population. In this case, the content of those micronutrients can be much lower than the FFL, without compromising the supply to ample sectors of the population.

Table 19.3 shows that for iron fortification of flours, the factor that limits the content of iron is of a technological nature, namely the incompatibility between the iron compounds and the food matrices. Addition of iron must be low to prevent undesirable changes in the sensorial properties of the flours. Thus, ferrous sulfate, which is water soluble and highly reactive, can be added in amounts around 25 mg/kg of iron in a low extraction wheat flour (highly refined, and low in fats). Less reactive iron compounds, such as ferrous fumarate and elemental iron of different types, are usually incorporated in amounts of 50 mg/kg of iron. However, in high extraction flours (whole or unrefined flours), the content of any type of iron is lower because of the presence of fats and other substances that cause rancidity and changes in color.

The addition of NaFeEDTA to bakery refined flour is still under investigation after a study reported interference of bread making by the EDTA moiety (19). Even though NaFeEDTA was

Table 19.3: Technical restrictions in the addition of iron reduce the estimated bioefficacy of fortified flours for women of reproductive age.

	Low extraction flour in an intermediate bioavailable diet (10%) for dietary iron)			High extraction flour in a low biovailable diet (5% for dietary iron)		
Iron compounts	Possible iron content (mg/kg)	Approximate EAR and RNI for women (mg/day)[1]	% EAR and RNI supplied in 100 g/day flour consumption	Possible iron content (mg/kg)	Approxiamte EAR and RNI for women (mg/day)	% EAR and RNI supplied in 100 g/day flour consumption
NaFeEDTA	-	-	-	20	14.1 and 29.4	14 and 7
Ferrous fumarate	45	14.1 and 29.4	32 and 15	25	28.2 and 58.8	9 and 4
Ferrous sulfate (dry)	25	14.1 and 29.4	18 and 9	-	-	-
Electrolytic iron	50	21.6 and 45.0	23 and 11	40	43.2 and 90.0	9 and 4
Hydrogen reduced iron	50	28.2 and 58.8	18 and 8	40	56.4 and 117.6	7 and 3

[1] EAR and RNI values for electrolytic and hydrogen reduced irons are estimated as 65% and 50% as ferrous sulfate, respectively, following data of relative bioavailability (11).

found to be compatible with flour destined for making bread, the amount of iron from this source would be restricted to around 35 mg/kg, considering that currently the maximum recommended intake of iron from NaFeEDTA is 0.2 mg iron/kg body weight per day (20). This maximum iron content from NaFeEDTA is estimated assuming 400 g/day as the largest flour consumption by a 70 kg person. Due to the better bioavailability, 35 mg/kg iron content from NaFeEDTA would provide a larger proportion of the EAR to women than 45 mg/kg of iron from ferrous fumarate in a diet low in iron absorption inhibitors (37% EAR against 32% EAR, respectively, when flour consumption is 100 g/day). However the cost would double, from $1/MT[8] to $2/MT.

Data in **Table 19.3** shows that with the amounts of iron incorporated into flour, and when flour consumption is 100 g/day, the additional intake of this nutrient can be from 18–32% of women's EAR (or from 8–15% RNI[9]) using refined flours, and from 7–14% EAR (or from 3–7% RNI) using unrefined flours. The modest increments of additional iron intake from fortified unrefined flours raise doubts over the usefulness of fortifying these flours with iron. Similarly, iron fortification of other foods that would be consumed with meals rich in iron inhibitors may have low efficacy or would have low cost effectiveness because of the large quantities of iron that would be needed.

Nevertheless, flours can also carry many other micronutrients, and their role in improving one's nutritional status is potentially much higher than that for iron, as illustrated in **Table 19.4**. Flour consumption of 100 g/day of fortified refined flour is able to provide 70–100% EAR (60–85% RNI) of folate, vitamin B_{12}, and zinc; and 55–65% EAR (40–55% RNI) of vitamin A and all the other vitamins of the B complex. Similar intakes of vitamins A, and B_{12} and folate are obtained through the consumption of fortified unrefined flours. These flours provide lower amounts (15–45% EAR, or 10–35% RNI) of zinc and other vitamins of the B complex than the refined flours. This difference is expected given the lower addition of these nutrients in the fortification profile of unrefined flours. Because unrefined flours maintain important amounts of those micronutrients, the need for addition of micronutrients is smaller.

Assessing the potential nutritional implications

The WHO Guidelines on food fortification (4) suggest that the potential benefit of food fortification programs can be estimated by examining which proportion of the population moves from below to above the corresponding EAR values. It is not only difficult, but also rare, to estimate the distribution profile of EAR in populations from the usual diet. As a proxy, the calculation of the additional EAR obtained from fortified foods may be useful. In theory, the magnitude of the biological impact would correlate with the proportion of the additional EAR that is supplied. As a convention, it may be accepted that if a food provides at least 20% or 40% EAR[10], this food

8 MT=metric ton=1,000 kg.

9 Recommended nutrient intake (RNI) refers to the daily intake which meets the nutrient requirements of almost all apparently healthy individuals (97.5%) in an age- and sex-specific population group. It is set at the estimated average requirement plus 2 standard deviations (5).

10 This is similar to the recommendation given by the Codex Alimentarius (21) for nutrition claims, which specifies that if a food is a "source" of a specific nutrient if it supplies 15% of the Codex Nutrient Reference Values (NRV), which are similar to the Recommended Nutrient Intakes (RNI), per usual serving. In order to qualify as being "high" in a specific nutrient, a food product must contain twice as much of the nutrient as the "source" does. Excluding iron, the EAR values are approximately 80% of the corresponding RNI values.

Table 19.4: Cost and additional supply of micronutrients in fortified flours for women of reproductive age (assuming consumption of 100 g/day).

Micronutrient	Fortificant	Low extraction flour in an intermediate bioavailable diet (10% for dietary iron)			High extraction flour in a low bioavailable diet (5% for dietary iron)		
		Nutrient content (mg/kg)	Cost ($/MT)[1]	% EAR and RNI supplied [2]	Nutrient content (mg/kg)	Cost ($/MT)	% EAR and RNI supplied
Vitamin B_1	Thiamin mononitrate	6.0	0.19	67 and 55	2.0	0.06	22 and 18
Vitamin B_2	Riboflavin	5.0	0.19	56 and 45	4.0	0.15	44 and 36
Niacin	Niacinamide	60	0.61	55 and 43	15	0.15	14 and 11
Vitamin B_6	Pyridoxine	6.0	0.23	55 and 46	5.0	0.19	45 and 38
Vitamin B_{12}	Vitamin B_{12} 0.1% WS	0.01	0.42	100 and 83	0.01	0.42	100 and 83
Folate	Folic acid	2.0	0.20	106 and 85	2.0	0.20	106 and 85
Vitamin A	Retinyl palmitate (dry)	2.0	1.07	56 and 40	2.0	1.07	56 and 40
Iron	NaFeEDTA	-	-	-	20	1.00	14 and 7
	Ferrous fumarate	45	0.99	32 and 15	25	0.55	9 and 4
	Ferrous sulfate (dry)	25	0.20	18 and 9	-	-	-
	Electrolytic iron	50	0.23	23 and 11	40	0.19	9 and 4
	Hydrogen reduced iron	50	0.17	18 and 9	40	0.13	7 and 3
Zinc	Zinc oxide	30	0.15	73 and 61	20	0.08	24 and 20

[1] Cost = (micronutrient content in food x fortificant price) / (micronutrient proportion in fortificant x 1000)

[2] % RNI (or % EAR) = [(micronutrient content x food consumption) x (1 - % loss/100) / (1000 x RNI – or EAR –)] x 100. First value corresponds to EAR and second to RNI, when wheat flour consumption is 100 g/day.

could be considered as a "good" or an "excellent" source of the micronutrient, respectively. The importance of mass fortification as a public health program could be estimated by the absolute and relative number of individuals from the at risk groups whose consumptions reach those categories.

If the cost were disregarded, the most promising source of iron in refined flours is ferrous fumarate. Consumption of fortified wheat flour in amounts of about 125 g/day would provide 40% EAR (although only 19% RNI) to women of reproductive age. This iron compound may be replaced with electrolytic iron (type A-131) or ferrous sulfate if the consumption of flour is nearly or higher than 225 g/day. The only advantage of ferrous sulfate over the electrolytic iron is that it can be easily identified in the fortified flour. It is very difficult to guarantee that electrolytic iron (A-131) and not any other elemental iron of much lower bioavailability is being used (11, 22). The countries of Central America selected ferrous fumarate as the iron source to fortify wheat flour, not only because it has a good bioavailability (19), but also as a practical solution to guarantee that the flour contains a good iron compound.

In the case of unrefined flour, probably the only justifiable source of iron is NaFeEDTA, because of the potential to improve absorption of iron from other sources. However, the daily flour consumption should be larger than 150 g/day to supply at least 20% EAR (around 10% RNI) of iron to women of reproductive age.

How much additional iron is needed to have a biological impact?

All the prior considerations do not answer the question of how much additional iron is needed to obtain biological effects. **Table 19.5** attempts to respond to that query. The table summarizes published data of several efficacy and effectiveness studies on iron fortification interventions.

The study with refined wheat flour in Sri Lanka (25) failed to reduce the anemia prevalence in women of reproductive age, after two years of supplying a daily average of 12.5 mg of electrolytic (A-131) or reduced iron. This outcome can be easily explained by the small additional percent of EAR (22–29%), or RNI (11–14%), in a diet high in iron absorption inhibitors. Although this study could not determine serum ferritin, similar work in Bangladesh, supplying wheat flour fortified with reduced iron to 6–15 year old children for six months (30), found no changes in anemia. There were also no differences in serum ferritin and serum transferrin receptors between the experimental and the control groups. The experimental group had an additional intake of 6.6 mg/day of iron (25% EAR, or 20% RNI), and 300 mg/day of vitamin A (75% EAR). The prevalence of low retinol levels (<0.7 μmol/L or 20 μg/dL) changed from 13.6 to 7.4% in the experimental group, and from 15.4 to 22.5% in the control group. This result proved that wheat flour was a good fortification vehicle for vitamin A, but not for iron, especially within a population whose diet has low iron bioavailability.

Zimmermann and colleagues (26) recently published the results of an iron efficacy study that used snacks made with refined flour (40%), butter and margarine (25%), and sugar (22%). The snack was given to 18–50 year old Thai women six days a week over 35 weeks. The iron dose averaged 12–14 mg/day (estimated 46–92% EAR or 22–44% RNI, depending on the iron compound). The group treated with ferrous sulfate (92% EAR or 44% RNI) had a reduction of the anemia rate from 18 to 12%. The other iron compounds, electrolytic (A-131) and hydrogen reduced, did not produce a significant change in anemia rates. Nevertheless, both ferrous sulfate (92% EAR or 44% RNI) and the electrolytic iron (60% EAR or 29% RNI) improved iron stores measured by changes in serum ferritin and serum transferrin receptor. This study showed that both ferrous sulfate and electrolytic iron are absorbed and able to improve iron status. The effect correlated well with the proportions of EAR that were supplied. Here, it is important to point out that this treatment was applied in a diet free of iron absorption inhibitors, because the snack was given separately from meals.

Thuy et al. (27) reported an iron efficacy study using fish sauce fortified with NaFeEDTA in Vietnam. Women of reproductive age received 10 mg/day of iron (71% EAR or 34% RNI) over six months. The experimental group showed reduction in iron deficiency and iron deficiency anemia, but the change in total anemia prevalence was reported as not significant compared with the control group. A similar study conducted with soy sauce in China (31) reported reduction in anemia in all members of the family. However, low serum ferritin levels (<12 μg/L) were highly prevalent in all groups even after the period of treatment. This result, together with the relative low additional intake of iron (4 mg/day), makes the results of this study difficult to interpret.

The findings in Vietnam can be explained in several ways. First, the anemia may have been related to multiple factors other than iron deficiency, and hence the reduction was not as large as expected. Second, the period of exposure to the higher iron intake may have been too short. Finally, the iron dose may have been insufficient. The response of serum ferritin rules out infection as a reason for the lack of response. The period of exposure was likely adequate because a steady-state situation to a new intake of iron was reached during that period (32). In addition to the presence of multiple micronutrient deficiency, the most probable explanation for the lack of anemia reduction was that the additional intake of iron (71% EAR or 34% RNI) was still insufficient to reduce anemia in this population, although it was sufficient to start improving iron status. The results were comparable to the study using snacks that were fortified with electrolytic iron (60% EAR or 29% RNI) in Thailand.

An efficacy trial performed on school-age children of Morocco succeeded in demonstrating anemia reduction associated with the additional intake of iron, given as micronized ferric pyrophosphate in salt (28). Although the additional intakes of iron were similar to those in the studies made with women (7–18 g/day), given the lower iron requirements of the school-age children, it was determined that a larger biological supply of iron was reached: around 138% EAR (or 112% RNI).

Wegmüller et al. (29), from the same research group, made a similar study in Ivory Coast. However, in this case, anemia prevalence was not reduced. The authors attributed this outcome to the concomitant presence of malaria, and also probably to vitamin B_2 deficiency. However, this result can also be explained by the lower proportion of EAR supplied in this intervention trial: 65% versus 138% in Morocco (or 52% versus 112% RNI, respectively). It is interesting to note, that despite lack of response in anemia or iron deficiency anemia, iron stores were improved in the group of children receiving additional amounts of iron in Ivory Coast. This is a similar response to the women in Thailand who increased iron intake by 60% EAR (or 29% RNI) through the consumption of an iron fortified snack (26).

Data presented in **Table 19.5** suggest that, regardless of the fortified food and the iron compound used, the reduction of iron deficiency and iron deficiency anemia depends on the magnitude of the bioavailable iron. Obviously, the necessary amount of iron is influenced by the initial nutritional gap found in the population. In the studies reviewed, at least an additional intake equivalent to 60% EAR of iron was required to improve iron stores, and at least 90% EAR was needed to decrease nutritional anemia. Nevertheless, caution is needed to extrapolate this association to other populations, especially considering that anemia is caused by a multitude of factors and nutritional status varies widely in populations.

Table 19.5: Comparison of biological impact of iron fortification interventions (efficacy and effectiveness).

Food (country)	Target group	Iron compound	Additional intake of iron (mg/day)	Approx. EAR and RNI (mg/day)[1]	Additional % EAR and RNI	Anemia change[2] (%)	IDA[3] or (iron stores)[4] (%)	Iron content in food (mg/kg)	Dilution factor
Refined wheat flour (Sri Lanka)[a]	Women 32 ± 9 y, 2 years	Electrolytic (A-131)	12.5	43.4 and 90.0	29 and 14	27 to 24	No data	66	1:15,151
		Reduced	12.5	56.4 and 117.6	22 and 11	39 to 39	No data	66	1:14,545
		Control	0	-		30 to 32	No data	-	
Snack made with refined wheat flour (Thailand)[b]	Women 18–50 y, 6 days/wk, 35 wks	Ferrous sulfate		14.1 and 29.4	92 and 44	18 to 12[(**) c]	(34 to 7)[(**)]	562	1:569
		Electrolytic (A-131)	12–14	21.6 and 45.0	60 and 29	26 to 21[(*)]	(28 to 11)[(**)]	562	1:1,725
		Hydrogen reduced		28.1 and 58.8	46 and 22	20 to 18[(*)]	(30 to 21)[(*)]	562	1:1,708
		Control	0	-	0	19 to 20[(*)]	(39 to 30)[(*)]	-	-
Fish sauce (Vietnam)[d]	Women 17-49 y, 6 days/wk, 6 mos	NaFeEDTA	10	14.1 and 29.4	71 and 34	100 to 66.2	70 to 20** (70 to 33)*	1,000	1:130
		Control	0	-	-	100 to 89	69 to 58 (69 to 65)		

Food (country)	Target group	Iron compound	Additional intake of iron (mg/day)	Approx. EAR and RNI (mg/day)[1]	Additional % EAR and RNI	Anemia change[2] (%)	IDA[3] or (iron stores)[4] (%)	Iron content in food (mg/kg)	Dilution factor
Salt (Morocco)[e]	Children 6–15 y, 10 mos	Micr. ferric pyrophosph.	18	13 and 16	138 and 112	60 to 13**	30 to 5** (52 to 9)**	2,000	1:125
		Control	0	-	0	55 to 43	34 to 30 (55 to 57)	-	-
Salt (Ivory Coast)[f]	Children 5–15 y, 6 mos	Micr. ferric pyrophosph.	8.4	13 and 16	65 and 52	42 to 47	42 to 23* (58 to 28)**	3,000	1:83
		Control	0	-	0	62 to 62	62 to 38* (38 to 25)	-	-

[1] Using the WHO recommendations (4), and assuming iron bioavailability values as follows: ferrous sulfate: 10% in the snack made with refined flour and consumed separately from meals; electrolytic and hydrogen reduced irons in the snack estimated as 65% and 50% of ferrous sulfate, respectively, following data of relative bioavailability (11). Electrolytic and reduced iron of wheat flour consumed in meals estimated as 32% and 25% of ferrous sulfate in the snack, respectively. Ferric pyrophosphate bioavailability in salt was assumed as 34% of ferrous sulfate, based on a diet around 5% iron bioavailability (23), and that ferric pyrophosphate is around 70% as bioavailable as ferrous sulfate (12). NaFeEDTA bioavailability as 10% in fish sauce consumed with meals (24).

[2] Using the conventional WHO/FAO cut-off points for each age group.

[3] IDA = iron deficiency anemia.

[4] Serum ferritin concentration <15 μg/L (30 μg/L for Ivory Coast; 12 μg/L for Vietnam) or serum transferrin receptor concentration >8.5 mg/L.

[a] Data for calculations obtained from Nestel et al. (25), and assuming a diet 5% bioavailable for iron.

[b] Data for the calculations obtained from Zimmermann et al. (26), and assuming a diet 10% bioavailable for iron.

[c] Asterisks denote statistical difference from baseline: * P <0.02, ** P <0.001. Data belonging to the same group by logistic regression at P <0.05 are symbolized by: (*) and (**).

[d] Data for the calculations obtained from Thuy et al. (27), and assuming a diet 10% bioavailable for iron.

[e] Data for the calculations obtained from Zimmermann et al. (28), and assuming a diet 10% bioavailable for iron, and ferric pyrophosphate 70% as bioavailable as ferrous sulfate.

[f] Data for the calculations obtained from Wegmüller et al. (29) and assumptions same as above.

The analysis made illustrates the difficulty in improving iron status by means of iron fortification of flours, because the low amounts of bioavailable iron that are supplied (18–32% EAR in refined flours, and 7–14% EAR in unrefined flours), when flour consumption is around 100 g/day (see **Table 19.4**).

Information in **Table 19.5** is also useful to identify which types of food fortification were used in the studies. These examples cannot be classified as mass fortification, because the level of iron is very high, and consequently the dilution factor is very low. Thus, the iron contents were: snack with 652 mg/kg from different iron sources (26); fish sauce with 1,000 mg/kg iron from NaFeEDTA (27); and salt fortified with 2,000–3,000 mg/kg iron from micronized pyrophosphate (28, 29).

The estimated dilution factor for the snack was 1:569 to 1:1708, depending on the iron source. This figure, compared with the dilution factor of 1:14,545 or 1:15,151 of wheat flour fortified with iron (25), clearly shows that the snack was a special food and not one of mass fortification. The high content of iron and the special way that the product should be manufactured (highly processed food) makes this product an example of targeted fortification. Similarly, the other products included in **Table 19.5** should be manufactured by a reduced number of industries, under strict supervision, well packaged and labeled, and aimed at specific target groups. Under the usual rules of production and trade, these products cannot compete with the unfortified alternatives, not only because the relative difference in the cost is high, but also because of the complexities of handling large volumes of premixes and the low dilution factors. Nevertheless, these studies opened the possibility of effectively using target fortification as a valid strategy to reduce iron deficiency in poor communities.

Basic parameters for control and enforcement

The success of any micronutrient intervention depends on ensuring that the target populations receive the micronutrients in the amount and quality that are needed. Therefore, quality control and assurance actions by the producers, and inspection and enforcement by the public sector, is required to ensure that food fortification complies with expected standards (33, 34). In order to meet these requirements, it is important to establish values of reference and compliance criteria. This subject is frequently neglected and standards and regulations commonly do not reflect the realities of the fortification practice, both in terms of the variation process and the normal decay of vitamins during storage and distribution. Conflicts between the food industry and the public sector may arise when the public sector attempts to enforce unreasonable standards (33). **Table 19.6** introduces the basic production and regulatory parameters that can be used as reference for factory and legal compliance for fortified wheat flour of low extraction, when daily consumption pattern is from 50–200 g/day. In food production factories, the average content of each micronutrient in foods is calculated by adding the selected fortification content to the intrinsic content of the nutrient in the unfortified product. An acceptable range around the average should be estimated by means of subtracting and adding two coefficients of variation of the fortification process operating satisfactorily; those are the minimum and the maximum contents, respectively. In liquids, the variation of the fortification process is around 10%, but in solids it fluctuates between 12 and 30%, depending on the particle size, fluidity, and the relative amount of the added fortificant. The

[11] It is not equivalent to shelf life, which is the period that the food keeps the expected sensorial properties and it is safe to be consumed. Marketing time is the period that goes between manufacturing and purchasing of the product by the consumer. The marketing time might be much shorter than the shelf life.

Table 19.6: Basic parameters for food control and enforcement as applied to refined wheat flour fortified with several micronutrients.[1]

Micronutrient	Selected fortification content (mg/kg)	Intrinsic content (mg/kg)	Marketing losses (%)	C.V. of process (%)	Production parameters (mg/kg)			Regulatory parameters (mg/kg)	
					Minimum[2]	Average[3]	Maximum[4]	Legal minimum[5]	Tolerable maximum[6]
Vitamin B_1	6	0.6	15%	25%	3.3	6.6	9.9	3.0	N.A.
Vitamin B_2	5	0.5	10%	25%	2.7	5.5	8.3	2.5	N.A.
Niacin	60	10	5%	12%	53	70	87	50	N.A.
Vitamin B_6	6	0.4	10%	25%	3.2	6.4	9.6	3.0	N.A.
Vitamin B_{12}	0.01	0	10%	25%	0.005	0.010	0.015	0.005	N.A.
Folate	2	0.2	30%	25%	1.1	2.2	3.3	1.0	4.0
Vitamin A	2	0.0	30%	25%	1.0	2.0	3.0	0.8	3
Iron (total)	45	10	0%	12%	42	55	68	40	70
Iron (from fumarate)	45	0	0%	12%	34	45	56	30	60
Zinc	30	10	0%	12%	30	40	50	30	50

[1] This example is applicable when daily consumption pattern is from 50–200 g/day. If consumption is larger, fortification levels should be reduced.
[2] Minimum (mg/kg) = average x [1 - (2 x C.V. of fortification process (%)/100)]
[3] Average (mg/kg) = selected fortification content + intrinsic content
[4] Maximum (mg/kg) = average x [1 + (2 x C.V. of fortification process (%)/100)]
[5] Legal minimum (mg/kg) = minimum (mg/kg) x (1-marketing loss/100), and rounded.
[6] The Maximum Tolerable Level is the rounded value of the factory maximum. In the case of micronutrients whose Tolerable Upper Limit of Intake is not specified or very large, the regulation might be simplified by avoiding the inclusion of this parameter; i.e., non-applicable (N.A.).

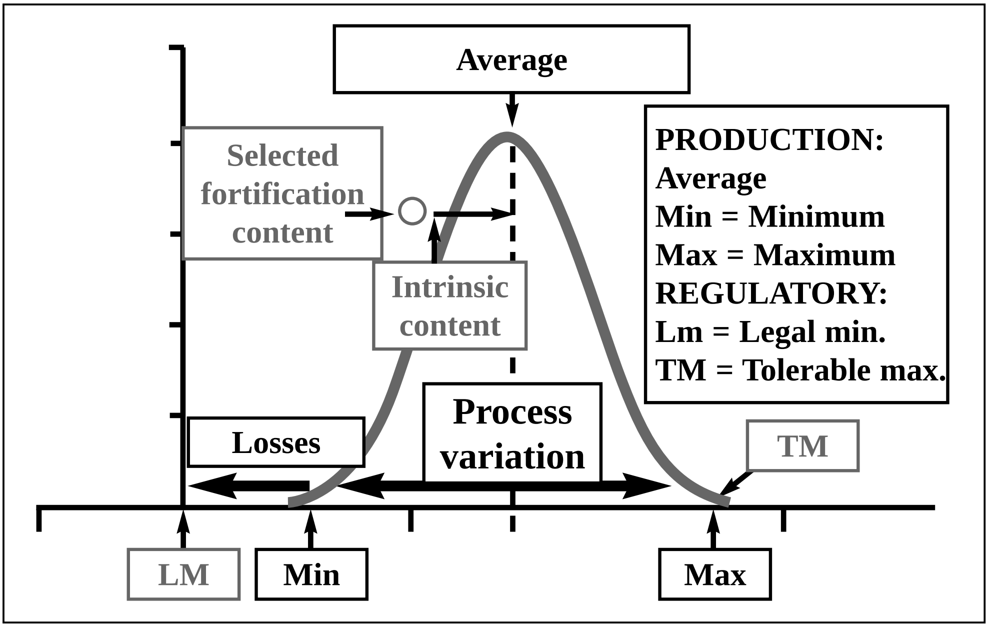

Figure 19.1: Production and regulatory parameters on food fortification. Quality control of fortified foods in factories aims to keep the micronutrient levels as near as possible to the **average** content (the selected fortification content plus the intrinsic content of the same micronutrient in the unfortified food), but always inside a range limited by the **minimum** (content calculated by reducing the average content by two coefficient of variation of the fortification process) and the **maximum** (content calculated by increasing the average content by two coefficient of variation of the fortification process). The regulatory parameters appear in the standards and on food labels, and support enforcement; they are the **legal minimum** (the minimum micronutrient content in the fortified food, which is calculated by reducing the usual losses of the micronutrient during normal conditions of distribution and storage within the marketing time of the food vehicle) and the **Maximum Tolerable Level** (the micronutrient content that coincides with the accepted maximum content at factories). The Maximum Tolerable Level may be excepted for micronutrients with very large or unspecified UL values of intake (figure modified from [4]).

acceptable ranges of fortification variation should be estimated for each food vehicle and for each micronutrient added.

In food standards, the expected rate of degradation of the vitamins in the product stored under acceptable conditions, within the usual marketing time[11] of the fortified food, should be subtracted from the factory minimum. The calculated value is in turn the legal minimum. In the case of those micronutrients whose intake is limited because of safety concerns, a tolerable maximum is also used. The value of this parameter should coincide with the factory maximum. Nutrients without UL recommendation may not present a tolerable maximum in order to simplify enforcement of the standards. Data in **Table 19.6** shows that it is normal to expect the tolerable maxima to be two to four times the value of the legal minima.

Figure 19.1 illustrates the relative position, in terms of nutrient content, of all the production and regulatory parameters described above. In practice, quality control and inspection cannot be done for each one of the added micronutrients to the food, and most of the times only one of them is used as the indicator. However, for this system to work properly, the micronutrient mixes and premixes should be certified. Experience has shown that mixes and premixes should also be included in standards and regulations (35). They also need to be supervised by the government authorities, because their quality determines the entire program's success. To estimate the content of micronutrients in the premix, one needs only multiply the selected fortification content of the fortified food by the estimated dilution factor. In turn, the calculated value becomes the minimum content of the micronutrients in the premix. Manufacturers of mixes and premixes may decide to add an overage (additional amounts to compensate for the expected losses) to guarantee compliance with the minimum content until the date of useful life that is claimed for mixes and premixes. Following the procedure described above, there is no need to calculate overages for the fortified food.

Certification of mixes and premixes is required not only for the micronutrient amounts but also for the quality. Poor quality vitamins degrade much more rapidly than high quality ones. In the case of minerals, especially elemental iron, the relative bioavailability depends not only on the type and quality, but also in the specific manufacturer (11, 22). Microbiological safety is another parameter to be checked in the micronutrient mixes and premixes.

All types of food fortification should follow official standards, and compliance should be monitored by the government. Fortification outside the range of the standards should never be permitted, as consumers do not have control over the additional micronutrient intakes. In the case of mass fortification, the very wide coverage of the intervention demands that standards should be followed strictly. In most countries, mass fortification is triggered by compulsory governmental regulations, although application of these may be limited only to the industrially manufactured foods and not to the domestically produced options.

Conclusions

Food fortification and dietary supplementation are alternative and complementary delivery systems that can increase the intake of micronutrients deficient in the diet. Efficacy depends on the amount and quality of the supplied micronutrients, regardless of the type of intervention. In the case of food fortification, the presence of absorption inhibitors in the diet, especially those based on plant foods (36–38) increases the necessary amounts of minerals (iron, zinc, copper, and calcium) to be delivered. Dietary supplements have the advantage of being able to supply sufficient quantities of micronutrients in amounts tailored to target groups, but their disadvantages are low coverage and high cost. Mass fortification, when used under industrial settings, has the advantage of wide coverage and low cost, but the disadvantage that micronutrient intakes may be insufficient to bridge the nutritional gap of at risk subgroups of the population. Targeted fortification has an intermediate position between dietary supplementation and mass fortification; the mentioned constraints of mass fortification are less limiting, but coverage is lower and cost is much higher than in mass fortification. Market-driven fortification may have epidemiological influence only in Western societies, where the consumption of processed foods provides a large proportion of the dietary energy. This fortification strategy, without proper regulations, may increase the risk of providing excessive micronutrient intakes.

Correction of nutritional anemia in developing countries requires not only iron but also the intake of many other vitamins and minerals. The latter nutrients can be effective and efficiently incorporated into mass fortification.

Iron fortification is a very difficult, complex and expensive endeavor. Efficacy and effectiveness trials have shown that it is necessary to supply large amounts of iron in the meals of most developing country diets to obtain a beneficial biological response in communities affected by nutritional anemias. It may also be necessary to give the treatment independently from meals, especially when the diet is rich in iron absorption inhibitors. The high iron density in the food vehicles of the demonstrated successful fortification trials discussed here makes these products examples of targeted fortification rather than mass fortification. These kinds of products, as well as dietary supplements, appear to be a reasonable way to proceed to reduce iron deficiency anemia in developing countries. Funding such strategies and making them permanent and sustainable remains a challenge.

In developing countries, mass fortification may still be the most cost-effective strategy to bridge the nutritional gap for essential micronutrients other than iron. Iron fortification may work as well, if the diet is not rich in iron absorption inhibitors. However, it is important to emphasize that the technological feasibility of mass fortification is linked to foods produced by centralized and adequately developed industries. It involves using large dilution factors of the fortificant in the food, and the sensorial changes, micronutrient segregation, vitamin deterioration, and price increase should be kept within reasonable limits. The presence of reliable government supervision is usually essential to guarantee product quality. It is also critical to keep in mind the fact that the public health significance of mass fortification depends on the extent of the consumption of the industrially produced food by the population, as well as the frequency and amount of consumption by individuals. If those conditions are not fulfilled, then targeted fortification and dietary supplementation may be adequate alternatives.

Any type of food fortification should be government regulated and supervised. Inspection should be based on sensible standards that reflect variation of the process, and micronutrient decay during the marketing time of the food and when storage conditions are adequate. Factories should also implement quality control and auditing procedures, based on checking one or very few micronutrients. In order that such a system works, the quality of the micronutrient mixes and premixes must be certified.

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