SUCCESS OF THE MICRONUTRIENT FORTIFICATION OF CEREAL FLOURS IN VENEZUELA

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AN EVALUATION REPORT

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SUMMARY OF FINDINGS

This external evaluation of the multiple fortification of cereal flour in Venezuela was supported by the Micronutrient Initiative because of its significance for the global promotion of cereal fortification. Many countries have introduced national cereal micronutrient fortification, but there are almost no outcome evaluations. This report describes the successful use of fortification of cereal flours to reduce iron deficiency and anemia on a national scale. A 1992 national nutrition survey of children 7, 11, and 15 years of age among lower socioeconomic groups that included 78% of the population found a 37% prevalence of iron deficiency and 19% prevalence of anemia in Caracas and similar rates nationwide. This was a significant increase from a similar survey in 1990 and coincided with a deteriorating economic situation. Alarmed nutrition leaders persuaded the government to create a special commission for the enrichment of food that initiated a program to fortify all wheat flour with iron, thiamin, riboflavin, and niacin and all precooked maize flour with these nutrients plus vitamin A. At the start the maize flour, consumed as "arepas," provided 60 mg of ferrous fumarate per kg and around 15% of dietary energy while the wheat flour supplied 20 mg/kg of ferrous fumarate and abou t 28% of the energy in socioeconomic groups IV and V.

When the population of Caracas was re-surveyed in 1994, iron deficiency had decreased to 16% and anemia to 9% in the same socioeconomic and age groups. In 1994 one-third of the ferrous fumarate in the maize flour was replaced with elemental iron to reduce discoloration when arepas were made with hard water. In surveys in Caracas in 1987, 1988, and 1999 iron deficiency continued to decrease as judged by serum ferritin. Anemia rose again but not to 1992 levels. This was believed to be due to a further deterioration of diets with the continuing economic crisis. Between 1992 and 1997, the consumption of cereals, eggs, fat, and sugar decreased. Moreover precooked maize consumption decreased 27%. This was compensated in part by a 23% increase in wheat flour, but with a net decrease in vitamin A intake from fortification, a possible factor in its effectiveness in reducing iron deficiency.

The program was judged to have cut both iron deficiency and anemia in half in the first two years. It also helped to reduce the consequences of decreases in dietary iron and other micronutrients due to a further deterioration in economic status and dietary quality. The cost for the multiple wheat fortification without vitamin A was less than one cent U.S. per person per year and for the multinutrient maize fortification less than ten cents U.S. per year. The only direct government costs were for monitoring. The program was the result of a strong initiative from the national nutrition community, support at high government levels, and importantly, the cooperation of the milling industry. Every developing country will benefit from such an initiative and from the resulting drop in iron deficiency with its multiple adverse consequences for learning and behavior, physical capacity, and disease resistance. A fortification program of this type has the advantage of coverage of persons of all ages except for infants. The latter must

be reached by a separate program.

1. INTRODUCTION

Fortification of wheat flour with thiamin, riboflavin and niacin, calcium, and iron was introduced in the United States in the 1940s and in a number of other countries including several in Central America in the 1950s. However, there were no adequate baselines permitting an evaluation of their impact, and economic conditions often improved concurrently. It would seem to be obvious that increasing the intake of nutrients through fortification of a major staple would be beneficial where intakes of a nutrient were borderline or deficient for some part of the population. However, this cannot be assumed because the availability of the fortificants also needs to be established. In the case of the most critical nutrient, iron, some of the compounds used for many years because of their stability in foods subsequently proved to be biologically unavailable or much less available than previously assumed.

The pioneering work of Miguel Layrisse in Venezuela and Leif Hallberg in Sweden established not only the hierarchy of absorption of potential iron fortificants, but also the quantitative effects of inhibitors and enhancers in the diet. This made possible a classification of diets with low, medium, and high iron absorption that facilitated determination of fortificant levels and guided nutrition education efforts to improve the iron value of diets.

Between 1989 and 1990 the Center for the Study of Growth and Development in the population of Venezuela (FUNDACREDESA), under the leadership of its President, Dr. Hern·n Méndez-Castellano, conducted a national nutrition survey that revealed anemia to be a major public health problem in Venezuela. School children 7, 11, and 15 years of age averaged 28% iron deficient, and in girls at these ages it was 41%. These results represented a sharp increase from surveys done in 1978 to 1985 (FUNDACREDESA 1990) and were attributed to the worsening economic situation. Since the country had one of the leading centers in the world for research on iron absorption and iron deficiency, these findings were a major challenge. The National Institute of Nutrition (INN), under the direction of Dr. Miguel Osio-Sandoval, conducted a feasibility study of flour fortification.

The reputation and credibility of Dr. Miguel Layrisse, the leader of hematology research in the Venezuelan Institute for Scientific Investigation (IVIC), Dr. Méndez-Castellano, and Dr. Sandoval, Dr. José María Bengoa, Dr. Werner Jaffé, Dr. E. Lara Pantín and other national nutrition leaders convinced the President of the Republic to appoint a high level Commission for the Nutritional Enrichment of Foods (CENA).The Minister for the Family, a former UNICEF Regional Director for Latin America and the Caribbean, Dr. Teresa Albanez Barnola, became the chairman of CENA and the leading advocate for fortification in the cabinet. The members of CENA were outstanding nutrition and health leaders in Venezuela. Despite some significant opposition and controversy, Dr. Albanez and the prominent nutrition experts of CENA convinced the other ministers and the Government to support nutritional fortification of all wheat and precooked maize (PCM) flours. This action was greatly facilitated by the cooperation of the milling industry, whose representatives came forward with a proposal for the voluntary enrichment of wheat flour with thiamine, riboflavin, niacin, and ferrous fumarate that was accepted and later made compulsory.

As a result, in 1992 Venezuela embarked on an ambitious program to fortify all wheat and precooked maize flour for human consumption in the country with a multinutrient mix that included ferrous fumarate as a source of iron. Nutrition surveys by FUNDACREDESA in 1997, 1998, and 1999 provided evidence for the program's effectiveness in Caracas. Based on the above evidence the program was certified in 2000 by WHO/UNICEF as successfully implemented on a national scale. UNICEF has given strong support to the flour fortification initiative since 1997 including financial assistance for evaluation surveys and more recently for monitoring.

The report that follows summarizes how the support of government and industry was mobilized, standards established and maintained, and the results evaluated. The evidence presented indicates not only that the program was successful in reducing the amount of iron deficiency and iron deficiency anemia but also in increasing the dietary intake of the B vitamins added to the cereal flours. Moreover, the flour fortification provided these benefits at low cost. The prior research, program implementation, lessons learned concerning program advocacy and implementation as well as evidence of effectiveness are summarized in this report. This successful demonstration of the effectiveness of cereal fortification represents an important contribution of Venezuela to the world.

This document represents the cooperative efforts of two experienced external consultants and senior Venezuelan professionals responsible for initiating the fortification program. The consultants are especially grateful to Dr. Miguel Layrisse, Dr. Hernán Méndez Castellano, Dr. José María Bengoa from the Fundación Cavendes and Dr. José Félix Chávez from the National Institute of Nutrition. Dr. María Nieves García-Casal of IVIC and both Debora Comini and Leyda Gómez of UNICEF contributed importantly. The support of the Micronutrient Initiative of Canada and the Venezuelan Country Office of UNICEF made the mission possible. This activity is part of the advocacy efforts to promote and document multinutrient fortification of food staples by the United Nations University and the International Nutrition Foundation.

2. ABSORPTION OF IRON FROM DIETS AND FORTIFICANTS

The use of iron radioisotopes to study iron absorption from food started in Venezuela in 1965 with the addition of the isotope to the growing plant and / or animal to obtain intrinsically labeled materials. These studies (Layrisse and Martínez-Torres, 1983) determined the iron absorption from vegetables commonly consumed by the Venezuelan population, such as corn, rice, and black beans. Absorption of iron from these foods was approximately half of that obtained with wheat or soy and only one-fourth to one-sixth of the iron absorption from meat, poultry, or fish. It was also evident that absorption was higher for subjects with iron deficiency compared to healthy volunteers, indicating that iron absorption depends not only on the quality and quantity of iron administered, but also on the iron reserves of the subjects.

A collaborative study described the iron absorption from seven foods of vegetable origin and three foods of animal origin. This study was extended later to include seven new vegetable items and five foods of animal origin (Layrisse 1985). The information on iron absorption from a single food is useful since in underdeveloped countries this food item could be ingested as a major source of energy and nutrients. However, information about iron absorption from a complete meal provides more valuable information, since it allows the identification of enhancing or inhibiting substances present in the diet that modify iron absorption.

For this purpose, ten different Venezuelan diets were tested to evaluate iron absorption (Layrisse et al. 1990, Taylor et al. 1995). From the five socioeconomic groups classified, five of the diets were consumed by the two lowest groups, three by the middle group, and two by the medium-high group. Total iron absorption from the diets of the lowest groups was 0.8 mg, for the middle group 1 mg, and for those for diets from the medium-high group 2 mg. The two lower socioeconomic groups not only consumed less iron but what they did ingest was less available. The differences in iron absorption among the diets was due to differences in inhibitors, mainly phytates, and enhancers such as ascorbic acid and the heme iron in meat.

The 210 subjects studied were either iron replete, mildly or severely iron deficient. Absorption was proportionately higher for iron deficient subjects compared to iron replete subjects for the same diet.

3. IRON FORTIFICATION COMPOUNDS

For successful results from iron fortification, it is essential to select food vehicles that are consumed daily, an iron compound that is well absorbed, and establish laboratory control of the enrichment (Hurrell and Cook 1990, INACG 1982, INACG 1993, WHO 1968). In the case of the Venezuelan fortification program all three premises have been fulfilled. The precooked maize bread is consumed by all of the population (except for infants) in the form of arepas. This is also true for wheat flour in the form of bread or pasta. Iron bioavailability from ferrous fumarate has been demonstrated to be similar to ferrous sulfate when it is added to cereal flours (Hurrell et al. 1989, Martínez-Torres et al. 1991). The industrialized process for each flour permits full control of the fortification ingredients.

Ferrous sulfate is considered the “gold standard” for inorganic bioavailability, but it can produce unacceptable changes in food color and taste. Compounds with high bioavailability tend to be reactive in foods while compound that are not reactive generally have poor bioavailability.

Elemental iron powders as well as water insoluble sources, such as ferric pyrophosphate and orthophosphate, have been used for many years to fortify foods, mainly because they do not change physical properties of foods. The latter have been the iron compounds used in most countries to fortify wheat flour.

There is still controversy about the bioavailability of elemental iron due to the disparity of the results reported in the literature and the lack of information about physical and chemical characteristics of the iron powders used. There is a considerable body of evidence suggesting that bioavailability of elemental iron powders is poor (Elwood et al. 1968). Hallberg et al. (1986) reported a low and variable bioavailability of carbonyl iron, prepared by neutron irradiation, in man. The bioavailability of elemental iron powders depends in part on the particle size and manufacturing processes.

Pla et al. (1976) found good correlation between solubility and availability for the hydrogenreduced electrolytic and carbonyl iron. Cook et al. (1973) demonstrated, in wheat rolls, that reduced iron of a particle size <40 microns had a bioavailability of 8.6% compared with 9.1% for ferrous sulfate. Crosby (1978) found reduced iron of small particle size (5 mm) to be nontoxic and as effective as ferrous sulfate. As the particle size becomes smaller, both the risk of explosion when it is handled in the flour mill and the cost increase.

In Venezuela, the compulsory fortification of precooked maize flour started to reach the total population in February 1993. It contained 50 mg of iron as ferrous fumarate per kilogram plus vitamin A, thiamin, riboflavin, and niacin. The fortification of wheat flour began in August of the same year. This flour was enriched with 20 mg/kg of iron as ferrous fumarate, plus thiamin, riboflavin, and niacin.

During the first year of iron fortification the only adverse effect observed occurred in two regions of the country where hard water is used for making corn bread. It was noticed that the bread turned slightly dark the day after it was baked. This physical and organoleptic change was confirmed in the laboratory. Although hard water and cooking procedures were factors affecting only one percent of the population of these regions, they resulted in a change in the iron fortification pattern. From February 1994, the precooked corn flour was enriched with 30 mg/kg of iron as ferrous fumarate and 20 mg of electrolytic iron. This pattern of iron fortification has continued since without any further problem with the characteristics of the maize bread. The fortification formula for wheat flour has not changed since the beginning of the program.

4. BACKGROUND AND IMPLEMENTATION OF THE VENEZUELAN CEREAL FORTIFICATION PROGRAM

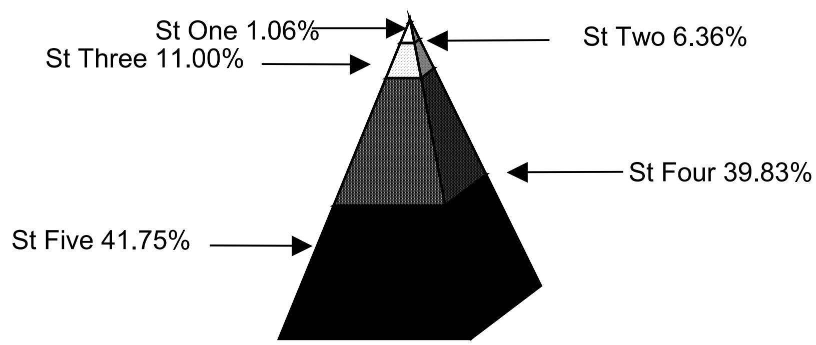
The severe economic crisis in Venezuela, which started in 1983, resulted in a progressive reduction in the quantity and quality of food consumed by people in the two lower socioeconomic strata, which includes over 80% of the total population (Méndez-Castellano 1990). In particular, because of high cost, the inclusion of meats in the daily diet must have been substantially reduced. As a result, there was a continuous increase in the prevalence of iron deficiency anemia (Layrisse et al. 1996). In 1989-90, FUNDACREDESA reported a 13% prevalence of iron deficiency and a 6% prevalence of anemia at the national level. A survey conducted in 1992 among children of the same age (7, 11, and 15 years) reported a 30% prevalence of iron deficiency and a 13% prevalence of anemia. Corresponding figures for children in Caracas were 37 and 19%, respectively (Méndez-Castellano 1996, Layrisse et al. 2001).

This situation motivated the National Institute of Nutrition (INN) to undertake a feasibility study for the fortification of precooked corn flour and wheat flour, staple foods consumed by all Venezuelans and, more importantly, accessible to the lower socioeconomic strata of the population.

In 1962 the Venezuelan maize industry successfully developed a precooked corn flour using the endosperm of maize after removal of germ and cuticle. The product was readily accepted since it had excellent flavor and properties that liberated housewives from the tedious task of preparing their traditional maize bread (arepas), a daily component in the diet of Venezuelans.

In 1991 during the economic crisis the two lowest of the five socioeconomic strata of the population were consuming, on a daily basis, about 110g and 85g of precooked maize flour and wheat flour, respectively (Chávez and González-Gamero 1998), making the two flours suitable carriers for a fortification program. As shown in Figure 1, the three lowest classes include 92% of the Venezuelan population. The top stratum contained 1.06% of the population and the second highest 6.36%.

Figure 1. Socioeconomic Strata of Venezuela in 2000



Within the group of cereals, food balance sheets reported in 1990 that the precooked maize flour provided 15% of the dietary energy and 11% of the available proteins. The precooked flour, however, had low quantities of thiamine, riboflavin, niacin, and less than 1 mg of iron per 100g (INN 1999). These attributes and characteristics made the precooked maize flour a very attractive vehicle for the fortification program in Venezuela.

Based on the recommendations of the INN for vitamin A, thiamine, riboflavin, niacin, and iron (Table 1) calculated deficits in these five nutrients varied from 31% for iron to 46% for riboflavin. It was decided, that the chosen carrier for the fortification plan should provide 25% of the daily recommended allowances established by the National Institute of Nutrition (INN 1985).

Based on a consumption estimate of 80g of precooked maize flour per person per day, and after adjusting for loss during preparation (30% vitamin A, 10% thiamine and niacin, and 5% riboflavin), the following enrichment profile per 100 g of flour was proposed for the precooked maize flour: vitamin A 270 RE, thiamine .31 mg, riboflavin .25 mg, niacin 5.1 mg, and iron 5.0 mg as ferrous fumarate (COVENIN 1996). These amounts provide 25% of the recommended allowances in 80 g of the flour for the lowest three socio-economic groups.

Table 1. DAILY ALLOWANCES, AVAILABILITY AND DEFICITS IN THE TYPICAL DIET OF VENEZUELA

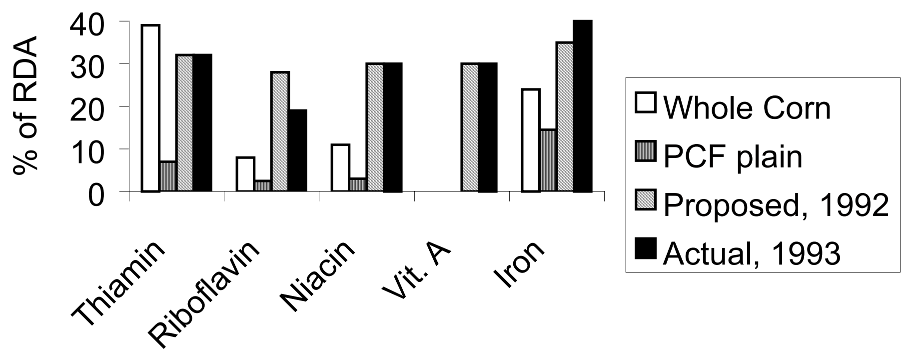
Nutrient	Daily Allowance (INN 1985)	True Availability (INN 1990)	Deficit %	25% of Allowances
Vitamin A, RE	612	358	42	153
Thiamin, mg	0.88	0.59	34	0.22
Riboflavin, mg	1.22	0.66	46	0.30

Niacin, mg	14.6	9.58	34	3.65
Iron, mg	14.0	9.72	31	3.5

RE=retinol equivalents.

A series of acceptability trials of the preparation of the typical maize bread (arepas), showed that "arepas" prepared with enriched flour in Caracas had no detectable changes in organoleptic characteristics and were readily accepted by samples of the target population. With these favorable results actions were begun to obtain the approval of the government for implementation of the program by the Ministry of Health and the National Institute of Nutrition and to inform producers of the desirability of fortifying the flour. The contribution of the pre-cooked maize flour (PCM) to the nutrient intakes of the three lowest economic groups is shown in Figure 2.

Figure 2. Nutrification of PCF in Venezuela
Average consumption: 91.6g/person/day
Strata Three, Four, and Five (1990-1996)

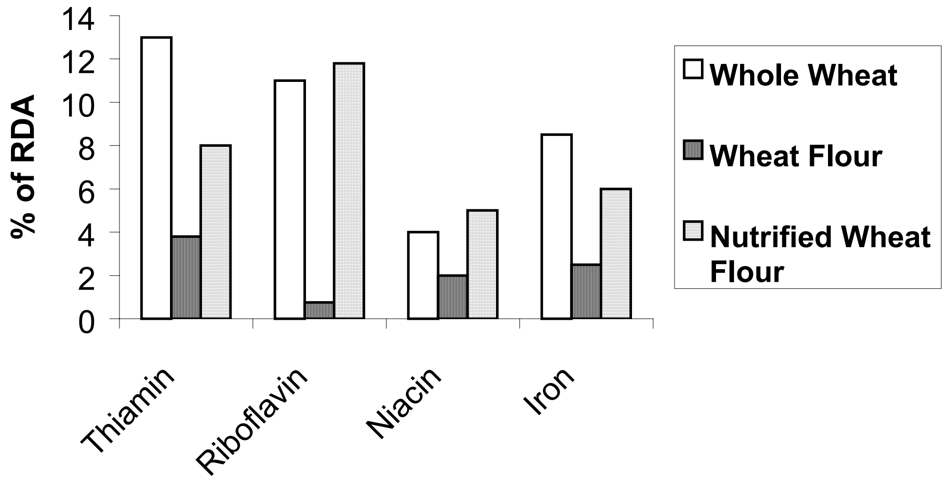


The announcement of the enrichment program as official policy provoked a diversity of opinions and reactions from both the industrial sector and individuals. To bring about agreement among all concerned, a special commission for the nutritional enrichment of foods (CENA) was created by a decree promulgated by president Carlos Andres Perez, and published in the official gazette in 1992 (Gaceta Oficial, 1992).

As originally appointed, CENA included one representative from each of four government ministries (Fomento, Familia, Sanidad y Asistencia Social, Agricultura y Cria), the Office of Coordination and Planning, the National Institute of Nutrition (INN), the Venezuelan Institute of Scientific Investigation (IVIC), the Venezuelan Chamber of Food Industry Norms (COVENIN), and the Venezuelan Council of Industry. Additionally, representatives from the industrial sector and recognized experts from different fields were called as needed. The Minister for the Family, Dr. Teresa Albanez-Barnola, played a crucial role in the process of promoting the cereal fortification program and was appointed president of CENA.

The CENA mandate was to bring about agreement among all concerned so that the cereal fortification programs could be launched as early as possible at the national level. After a series of meetings CENA was able to announce in February 1993 the mandatory character for the enrichment prescribed for all the precooked maize and wheat flour produced in the country. A similar path was followed earlier for the establishment of the voluntary fortification of wheat flour with the following profile in mg/kg: thiamine 0.15, riboflavin 0.20, niacin 2.0, and iron 2.0. The contribution of the wheat flour (WF) to the nutrient intake of the three lowest economic groups is shown in Figure 3.

Figure 3. Nutrification of WF in Venezuela Average Consumption: 25.4g/person/day Strata Three, Four and Five (1990-1996)



Because of a lack of evidence of a vitamin A deficiency problem in Venezuela and the greater cost, vitamin A was not included in the fortificant mix for the wheat flour. In each case primary reliance was on cooperation of the private industry in carrying out appropriate sampling and analysis of their products as produced. This was done and the INN has the detailed control data that they provide.

5. COSTS

The Venezuelan Association of Wheat Millers (ASOTRIGO) reported that the cost for start-up equipment (precision feeder and spectrophotometer) was about U.S. $ 16,000 for each of 16 plants producing the fortified wheat flour. Comparable costs for the pre-cooked maize (PCM) flour were not provided, but they should have been similar per factory.

Once the precision feeders and spectrophotometers for laboratory analysis were purchased there was little additional cost for the manufacturer except for the costs for the fortificant and for analysis of production samples. For wheat millers the annual cost of reagents and labor for analysis of the production sample was about U.S. $ 12,000. Again costs for analyzing PCM samples can be assumed to be similar. It should be noted that only iron was analyzed and served as an indicator of appropriate level and mixing of the fortificant.

Considering the average consumption of corn and wheat flour, the cost per kg of the vitamin-iron premix, and the amounts of nutrients to be added per metric ton of precooked maize and wheat flours, it was possible to estimate the cost of fortification in 1996 at $0.10 for the precooked maize and less than $0.01 for wheat flour per person per year. The difference is mainly the cost of the vitamin A that was included in the PCM but not in the wheat flour.

Initially there was no provision for point of sale sampling and analysis by the government, a weakness in the documentation of the program that is now being corrected. It is important that the government appropriate funds for point of sale monitoring fortification programs.

6. COMPLIANCE WITH FORTIFICATION STANDARDS

The Department of Food Hygiene (DHA) of the Ministry of Health and Social Development (MSDS) is responsible for the enforcement of compliance with the fortification norms by the producers of maize and wheat flours. At three-month intervals, DHA oversees the execution of the process at the production plants and the accurate registering of data required by standard quality control procedures.

The norms established for determining compliance with the mandated level of fortification are given in Table 2. Following prescribed standard operating procedures at each production plant, the regional services of DHA select samples of the fortified flours, which are submitted to the National Institute of Hygiene (INH“RR”) for iron analysis. Only iron determinations are carried out and reported to DHA for use as an indicator of compliance with the fortification norms.

Table 2. NORMS FOR COMPLIANCE WITH THE MANDATED LEVEL OF FORTIFICATION PER 100 GRAMS FLOUR (COVENIN 1994, 1996)				
Added Nutrient	**Maize Flour**		**Wheat Flour**	
	Minimum	**Maximum**	**Minimum**	**Maximum**
Vitamin A, RE	135	405	-	-
Thiamine, mg	0.20	0.50	.12	.18
Riboflavin, mg	0.16	0.40	.16	.24
Niacin, mg	3.3	8.2	1.6	2.4
Iron, mg	3.0	8.0	1.6	2.4

DHA discusses deviations from the iron fortification norm with the corresponding manufacturers and makes recommendations for their prompt correction and satisfactory compliance. Additionally, DHA schedules revisits in the following month to production plants that do not satisfy the norms in order to verify progress in the implementation of its recommendations.

With technical and financial assistance from UNICEF since 1997, and more recently from PAHO, a plan for monitoring the fortification program at the market place has been formulated and implemented as of January 2001. It will check to ensure that the required levels of the fortificants are reaching the consumer. A database has been established that continuously incorporates the information relating to the nutrient content of the enriched flours. The basic information is obtained by chemical analysis of the fortified flours for their nutrient content. The results are evaluated for compliance and presented as public information.

Existing resources of INN are used for the execution of the program, making it difficult to estimate its true cost. The Nutrition Units (NU) of INN in the capital of each of the 24 states of the nation have the responsibility of collecting maize and wheat flour samples in accord with defined procedures and specific sampling schedules established by INN through SISVAN for 2001. Lic. Rebeca Lares is in charge of SISVAN.

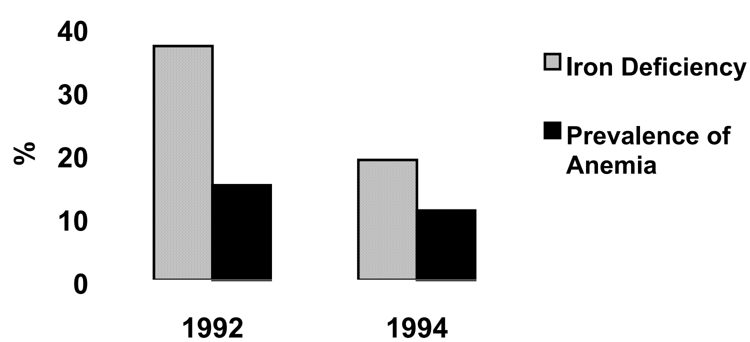
A package of each of the flour brands available in a specific commercial establishment, as designated in the SISVAN monthly generated schedule, is purchased by local personnel and forwarded to the "División de Investigaciones en Alimentos (DIA)" of INN in Caracas. Chemical analyses are performed under the direction of Dr. José Félix Chávez and results evaluated by comparison with the COVENIN norms. In this case the results for all nutrients are used for estimating added contributions from the fortified flours to the regular diets. Pertinent reports with appropriate recommendations are prepared by SISVAN and distributed to the NUs of INN in each state and made available to interested public. Early results (January 2001) obtained in this process and provided by INN show 88% and 77% compliance in the fortification of maize and wheat flours, respectively (Chávez, JF and Gónzalez-Gamero, E, Personal Communication, 2001).

When corrective action is indicated, the office of the Executive Director of INN sends the pertinent information to DHA for appropriate action. The information is also made available to the "Cámara Venezolana de Productores de Maíz (VENMAIZ)" and the "Asociación de Molinos de Trigo (ASOTRIGO)"

7. RESULTS OF THE VENEZUELAN CEREAL FORTIFICATION PROGRAM

In 1994, one year after the beginning of the flour fortification program, a survey in Caracas of 317 children, aged 7, 11, and 15 years, showed a significant reduction of iron deficiency and anemia to 15 and 10%, respectively, from the original corresponding values (37 and 19%) reported in the 1992 survey of children of the same age in Caracas (See Figure 4). The results of the 1994 survey also showed a statistically significant increase in ferritin from 15 μg/L in 1992 to 22 μg/L (Layrisse et al. 1996).

Figure 4. Impact of the nutrification program
Metropolitan area of Caracas



Source: Layrisse, M *et al. Am. J. Clin. Nutr.* 1996

The pioneering research of Layrisse and his collaborators (Layrisse et al. 1997, 2000, García-Casal et al. 1998, 2000) found that vitamin A improved the absorption of iron from a breakfast meal of maize bread and coffee. Others in Guatemala (Mejia and Arroyave 1982, Mejia and Chew 1988) and Indonesia (Bloem et al. 1989, 1990, Suharno and Muhilal 1996, Suharno et al. 1993) reported that vitamin A improves iron status. It is possible, therefore, that the vitamin A in the enriched precooked maize flour may have contributed to the absorption of iron from the diet. However, this has recently been investigated using modern stable isotope technology with meals similar to those used by Layrisse, and the report is soon to be submitted for publication (Richard Hurrell, personal communication 2001). In two studies in Zurich with Leif Hallberg and three in Göttenberg no effect on iron absorption was found. Differences in the degree of iron deficiency may be a factor.

With financial and technical support from UNICEF, it was possible to conduct surveys for evaluating the impact of the fortified flour program on Venezuelan children, adolescents, and adults towards the end of 1997 and again in mid-1998 and 1999. The children included in these surveys were selected at random, following well-defined uniform procedures that used national census data to construct the sampling frames. Results for the baseline population (children 7, 11, and 15 years old), again document improvement of the iron deficiency and anemia problem of Venezuela (Layrisse et al. 2001). In 1998, only 11.2% of 478 children in the Caracas baseline population (7, 11, and 15) were iron deficient and 18.6% of 466 children were diagnosed anemic, essentially matching the prevalence rate of anemia in 1992.

A similar result was reported for the survey in 1999, when 15.5% of 537 children were iron deficient and 17.1% of 545 children were classified as anemic. Iron reserves continued to increase as documented in Table 3 by the ferritin values of 24 and 28 μg/L in 1997 (n=571) and 1998 (n=466), respectively. The ferritin value for the 537 children surveyed in 1999 was practically the same as that reported in 1998, 27 μg/L (FUNDACRESA 1998, 1999, Layrisse et al. 2001).

Table 3. FERRITIN LEVELS IN CHILDREN FROM THE LOW SOCIOECONOMIC STRATA OF THE VENEZUELAN POPULATION. RESULTS FROM FIVE SURVEYS (LAYRISSE ET AL. 1996, LAYRISSE ET AL. 2001)

SURVEY	N	Mean*	SE	Median	95% CL
1992	282	13.46[d]	1.05	15	12.2-14.8
1994	317	20.54[c]	1.04	22	19.0-22.2
1997	571	21.91[a,b,c]	1.03	24	20.5-23.4
1998	466	26.08[a]	1.26	28	24.3-28.0
1999	537	24.10 [a,b]	1.03	27	21.0-24.3

*Geometric mean. Mans without common letters differ statistically, p< .001 SE = Standard error.

In summary, the results from the five surveys conducted in the 1992-1999 period show a significant reduction in the prevalence of anemia as well as in the proportion of children with evidence of iron deficiency in Caracas one year after the fortified flours were made available to the population. There were no significant differences for anemia or iron deficiency in the last three surveys: 1997, 1998, and 1999 (Layrisse et al. 2001).

8. CRITICAL CONSIDERATIONS

The evidence presented (Tables 3 and 4) indicates a dramatic reduction in 1994, one year after the fortification program was initiated. The prevalence of anemia in children dropped almost in half and their iron stores as indicated by ferritin increased to the same extent. In subsequent surveys in 1997, 1998 and 1999, the ferritin values continued at the level of 1994 and even showed a slight further increase, but anemia as judged by hemoglobin values returned to prefortification levels. This latter clearly was not the desired outcome and needs further consideration.

Table 4. PREVALENCE OF ANEMIA AND IRON DEFICIENCY IN CHILDREN FROM THE LOW SOCIOECONOMIC STRATA OF THE VENEZUELAN POPULATION. RESULTS FROM FIVE SURVEYS (LAYRISSE ET AL. 1996, LAYRISSE ET AL. 2001)						
SURVEY YEAR	**POPULATION**	**ANEMIA**		**POPULATION**	**IRON DEFICIENCY**	
		N	%	N	N	%
1992	282	51	19.0	282	105	36.6
1994	317	30	9.3	317	50	15.8
1997	590	86	14.6	571	80	14.0
1998	478	89	18.6	466	52	11.2
1999	545	93	17.1	537	83	15.5

The sampling procedures were the same in all years and the sample in 1994 was slightly larger than in 1992 although not as large as those of 1997 to 1999. Given the sample size, a sampling error of the magnitude of the 1994 decrease in anemia and increase in iron stores is all but statistically impossible. The reviewers searched in vain for any difference in the hemoglobin assays in 1992 from previous or subsequent years that could account on the basis of analytical error for this very significant drop in the first years after fortification and a later increase.

The fact that iron stores as judged by serum ferritin improved after fortification proportionately as much as the hemoglobin levels is further indication that the decrease in anemia was not an analytical error. But why did anemia increase again despite continued fortification? The Venezuelan investigators place major emphasis on the continued deterioration of economic conditions in the country and believe that anemia would have been much worse without the program.

As evidence for the effect of deteriorating conditions on nutritional status, the investigators cite a drop in the consumption of eggs, fat, and sugar between 1992 and 1997 and a 27% drop in consumption of the precooked maize which is relatively more expensive than wheat (Garcia-Casal 2001). This was only partially replaced by an increase of 23% in wheat flour consumption. They also suggested that a sharp increase in viral infections might have played a role.

Substituting elemental iron of possibly lower bioavailability for some of the ferrous fumarate in the fortified maize flour could have been a factor. However, it was electrolytic iron of presumably good availability. In any case the effect of this change is confounded by two other factors. As noted above, in the later years, corn flour consumption decreased, and that of wheat flour increased. This would have diluted any effect of the use of elemental iron for part of the fortification of the maize flour. However, it would also have affected vitamin A intake since this nutrient was not included in the fortificant mix for the wheat flour. The drop in precooked corn flour consumption would have decreased the vitamin A supplement by 22% (Garcia-Casal 2001). As suggested by the eleven references in Section F, vitamin A intake or status is related to iron status.

Questions have been asked as to why the analysis is only for children 7, 11, and 15 years old when extensive data on all ages were obtained in the later surveys. The limited resources for the 1994 survey forced the investigators to choose what they considered representative age groups of children and confine the survey to Caracas. Among the recommendations of this report is that additional resources be mobilized for further analysis of the very extensive clinical, anthropometric, dietary, and laboratory data obtained nationally in 1996 for all ages and completely tabulated in the three volume Fundacredesa report (M■ndez-Castellano 1996).

9. PERCEIVED ADVANTAGES OF THE VENEZUELAN CEREAL FORTIFICATION PROGRAM

The advantages of a universal cereal fortification program were perceived to be:

1. Almost complete direct coverage of the population except for breastfed infants after 4 to 6 months. Younger infants still benefit from improved iron stores as a result of better iron status of their mothers.
2. Results could be expected in a relatively short time, perhaps a year.
3. No modification of dietary habits was required. To achieve a comparable improvement in iron status in the face of the deepening economic crisis by promoting dietary improvement was considered impossible.
4. Fortification is internationally acceptable, could be promoted by law, and could be expected to be effective.
5. The cost was relatively low and did not require large government expenditures.
6. The cost was judged to be very small in relation to the potential benefits.

Possible problems that were identified and found resolvable included:

1. Selection of the appropriate food vehicles.
2. Selection of an appropriate iron compound for addition to the flours.
3. Obtaining the support and commitment of the cereal milling industry.
4. Obtaining the necessary legislation requiring universal multiple fortifications of the selected vehicles.
5. Enhancement of milling technologies to include fortification.
6. Ability to obtain the fortificant premix at reasonable cost. Providing for adherence to standards and continuous monitoring of the quality of the products.

10. SPECIAL FEATURES OF THE VENZUELAN CEREAL ENRICHMENT EXPERIENCE

There are a number of features that are unique to the Venezuelan experience, but that can be adapted to the introduction of fortification in other countries. These include:

1. Sustained support from the Director of the National Institute of Nutrition, the Director of FUNDACREDESA, and the Director of the Hematology Research group in IVIC and their respective staffs.
2. Ability of this group to persuade the President of the Republic to establish by official decree a Commission for the Nutritional Enrichment of Foods (CENA).
3. Support of a group of well-known and respected Venezuelan leaders in human nutrition and public health as members of CENA who were able to convince the government authorities of the importance of the compulsory multiple nutrient fortification of wheat and precooked maize flour.
4. A Minister of the Family, who took up the issue as a personal crusade, recruited other cabinet ministers and chaired CENA.
5. Visit of a CENA task force to the President of the Republic that convinced him of the need for a compulsory program.
6. Private sector cooperation and support from the wheat millers and key representatives of the maize processors supported the effort from the beginning and the flour millers actually came forward with a proposal for voluntary fortification of wheat flour that was accepted by the National Institute of Nutrition and later made compulsory upon the recommendation of CENA in which representatives of both groups participated.
7. Meetings with the Venezuelan Chamber of the Food Industry (CAVIDEA) that obtained their support.
8. A special one-day conference sponsored by the food industry in 1992 with the participation of decision-makers, nutrition leaders, and food scientists from the country and from abroad that built consensus.
9. Open and continuous debate and publicity in the mass media. This should not be underestimated since it generated interest and support for the program and helped to dissipate opposition.
10. Favorable characteristics of the selected vehicles, both wheat and precooked maize flour. In particular the popular maize arepa, unique to Venezuela, had some of the image of a superfood that could be further enhanced by fortification.
11. Although directed primarily at the problem of iron deficiency, the multiple fortification formula was an added benefit. Moreover, the addition of vitamin A to the fortificant mix for the precooked maize flour almost certainly improved the absorption of the added iron.

Factors less favorable for the program were:

1. Dependence on an imported premix, although available from seven vendors in six countries.
2. Difficulty in obtaining funds for standardization and monitoring.
3. Darkening of the arepas in certain regions with the original fortificant mix.
4. Some initial difficulty in obtaining homogeneity of the fortificants in the premix and final product.
5. There was no program to inform the public of the serious risk of micronutrient deficiencies, particularly that of iron, or that the two flours were fortified. While this was not a deterrent to the acceptance and effectiveness of the program, an opportunity for nutrition education was lost.

11. LESSONS LEARNED

1. While strong consensus and support from the nutrition and public health community is the key to the successful promotion of a nutrient supplementation program, it is also necessary to mobilize the political support at high government or parliamentary levels to obtain the necessary legislative action and funds required for quality control and monitoring.

2. The costs of fortification at the factory are extremely low, expressed either as costs per person per year or as percent of product cost. Obviously, the larger the population of a country and the number of mills, the higher will be the total initial investment for universal fortification. Moreover, in calculating the costs of a fortification program the costs of monitoring and evaluation are significant and must be taken into account.

3. In planning fortification programs a mechanism and funding must be built into the government budget to obtain representative samples at the point of sale on a regular basis and analyze them for compliance with the established fortification levels. These are not a substitute for the essential analysis at the point of manufacture using an appropriate sampling routine. Provision should be made for the results to be supplied periodically to the government institution that is responsible for monitoring the program and that institution should evaluate them promptly in order to follow up problems encountered.

4. Experience with minor color change in maize arepas prepared in regions with exceptionally hard water indicates the need for the monitoring institution to take note of any consumer complaints when samples are taken for control analysis at the point of sale.

5. The prompt publication of the results of research studies related to the project in international scientific journals has proved valuable in attracting attention to the program and mobilizing support of the scientific community. Unpublished government reports are not a substitute for peer review by the scientific community.

6. Baseline surveys are important to establish the population status for nutrients to be included in the fortification program. It is possible to evaluate the impact of the Venezuelan program on iron status because good baseline data on biological indicators are available. However, no such data exist for the B vitamins included so it is impossible to determine if their status also

improved. Before adding folic acid to the fortificant mix, baseline surveys must be carried out to determine serum folic acid levels. If possible, a sample of serum homocysteine levels would also be desirable.

12. PRIORITY RESEARCH NEEDS

A series of urgent research needs were identified:

1. An opportunity was lost to evaluate the effects of the B-vitamins in the original fortificant mix. With the plans to add folic acid to the mix it is important to obtain baseline data on serum folic acid levels as well as to calculate current dietary intakes of folic acid that will permit evaluation of the effect of the fortification on folate status. Information on the folic acid content of diets is also desirable.
2. The current fortification program can contribute to the prevention of iron deficiency in early infancy by improving iron stores received from mothers. However, it does little to correct iron deficiency anemia in children 6 to 18 months of age when the developing brain can be damaged. There is an urgent need to find feasible means of improving the iron intakes and iron status of this critical age group.
3. Ferrous fumarate proved to be a satisfactory fortificant except where the water supply was exceptionally hard. It was necessary to substitute partially with the less available electrolytic iron. There is a need to explore other compounds that might fulfill the solubility, stability and bioavailability requirements under these conditions without a change in food characteristics.
4. The absorption of iron from PCM fortified with ferrous fumarate alone should be compared with that for the mixture of ferrous fumarate and electrolytic iron subsequently adopted. This will help in interpretation of the program results.

13. CONCLUSIONS

There are a number of important conclusions from the Venezuelan experience:

1. The fortification of cereal flours with a suitable iron compound plus selected B vitamins is a feasible, effective, and relatively low cost method of improving iron status and increasing the dietary intake of the added vitamins.
2. On the basis of the experience reviewed in this report appropriate micronutrient fortification of cereal flours is highly recommended for all countries that have a portion of their population deficient or borderline in iron and some vitamins. This is true not only for all developing countries, but also for many industrialized ones.
3. Fortification of cereal flour with iron and other micronutrients will reduce the prevalence of iron deficiency anemia and iron deficiency but will not eliminate them. It is simply not practical to get enough iron absorbed by this approach to meet all needs. In addition when iron deficiency anemia is reduced, anemia due to other causes becomes more evident.

4. Once the mechanisms for iron fortification are established the additional cost of a multinutrient fortificant mix is minimal. As is already the practice in most countries with cereal fortification programs, fortification should provide not only iron but also a basic mix of B vitamins and possibly additional minerals.
5. It was fortunate that one of the vehicles selected for fortification, the maize flour, was precooked. This facilitated the addition of vitamin A without significant loss of it during processing. However, it increased the cost from one cent to ten cents US per person per year. Because the loss of vitamin A in baking bread can be as much as 80%, the cost of adding vitamin A to the wheat flour was judged prohibitive. In countries where there is not a precooked cereal staple to which vitamin A might be added, it would be important to ensure that margarine and cooking oils are fortified with vitamin A.
6. The contribution of the vitamin A added to the precooked maize flour to improvement in hemoglobin levels could not be assessed. However, in attempting to extrapolate the results of the multiple fortification of cereals in Venezuela, it is worth noting that the contribution of maize and wheat to total diet was less than 40% of the protein (Méndez-Castellano 1995). Among lower income groups in poorer developing countries the percentage is much higher (e.g., 60% in Pakistan (Hussein 1999), 63% In China (Zhao 2000), and up to 64% in Guatemalan highland villages (Flores and Reh 1955).
7. The scientific community, particularly individuals and institutions concerned with nutrition and public health, must take the lead in convincing politicians at the highest level to take the necessary actions to assure fortification and they must provide technical guidance at every step in the process, including follow-up. However, success will depend on their ability to enlist strong political support and to obtain acceptance by the private sector.
8. The process for establishing fortification of foods is facilitated by a strong nutrition research community within the country. The availability of convincing data on the magnitude of micronutrient deficiencies in Venezuela provided by FUNDACREDESA, INN, and IVIC was instrumental in convincing government authorities of the need and potential benefits of reducing iron and other micronutrient deficiencies through fortification of appropriate staple foods. So did the internationally recognized research results of Miguel Layrisse and colleagues on the availability of iron from diets with and without fortification, especially at low-income levels.

14. RECOMMENDATIONS

1. For the control of iron deficiency in vulnerable groups cereal fortification needs to be complemented by supplementation of pregnant women and infants 6 to 18 months of age. Breastfed infants born of moderately to severely anemic mothers or born with low birthweight will need complementary iron earlier.
2. Recent evidence has led the United States and an increasing number of other countries to add folic acid to the fortificant mix in order to reduce the prevalence of neural tube defects and elevated homocysteine levels. Present plans to include folic acid in the mix for flour fortification in Venezuela should be given a high priority, as is now the case in other Latin

American countries that already have or are planning multinutrient fortification. However, before this measure is implemented baseline biological data that reflect folic acid status should be obtained to allow for later impact evaluation. Data on the folic acid content of representative diets would also be useful for interpreting results.

3. Research studies in some developing country populations are finding an improvement in child growth and immune status with zinc supplementation. While there is no good evidence of the magnitude and distribution of zinc deficiency or even a reliable method for determining it, the response to these population specific intervention studies suggest that it may be more common than previously suspected. Since the cost of adding it to the fortificant mix is essentially zero, this should be seriously considered.
4. Program monitoring of the nutrient content of the product at the point of sale has been started but should be expanded and made permanent.
5. In the interests of the future health of the population of Venezuela it is extremely important that the government invest more in the evaluation research and monitoring of this project. If this were to be provided additional external support for specialized studies of value to other countries would be desirable provided suitable detailed proposals are prepared, submitted, and favorably peer reviewed.
6. There is an urgent need to upgrade the standard reference laboratories in order to improve their capacity for analysis of flour samples not only for iron but also for vitamin A and B vitamins. This is essential for proper monitoring of the enrichment program.
7. Updated information on the distribution and status of the companies responsible for producing the wheat and precooked maize including storage conditions installed and utilized production capacity and annual production should be collected at regular time intervals.
8. A government budget should be established for the surveillance and monitoring of the fortification program through information obtained from the milling companies and from analysis of samples at the point of sale.
9. Even exclusively breastfed infants are extremely vulnerable to iron deficiency and its serious functional consequences once iron stores from the mother are exhausted. There is a need to explore ways of supplying iron to young children particularly those between 6 to 18 months of age, other than by commercially fortified cereal products that are generally too costly for low-income families.
10. While fortification of flour is important for improving the nutrient status of the mother before pregnancy it is not sufficient for the needs during pregnancy when the basic diet is poor. Supplementation is recommended for this vulnerable group.
11. In 1996 FUNDACREDESA published three volumes filled with data on human growth and development of Venezuelan children up to 19 years of age. Data published by FUNDACREDESA (1996) give the weight, height, arm area and fat area of children in Caracas and the rest of the country. These data indicate that boys 1 to 2 years of age with anemia in Caracas were 2.4 cm shorter and 0.6 kg less in weight than those with normal hemoglobin. At 3 to 5 years of age the differences were greater. For 1 to 2 year old boys in

the remainder of the country comparable differences were 0.4 cm and 3.1 kg. For boys age 3 to 5 years they were 2 kg and almost 5 cm. For girls 3 to 5 years of age the differences were 1.2 kg and 6 cm. Such observations are important and should be analyzed and published to document the adverse developmental effects of low hemoglobin. They should also be compared with data obtained before the start of the fortification program.

12. The plan to expand the fortification of the two flours to include folic acid provides a new opportunity to introduce educational and media information on the advantages of the fortification program and the reasons for it.
13. The very extensive research of IVIC on iron absorption and fortification, the extensive data collected by FUNDACREDESA and studies by the INN were instrumental in obtaining political and technical support for the program. This type of research should be continued and strengthened.

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18. ORGANIZATIONAL ACRONYMS USED IN THE REPORT

ACC/SCN	United Nations Administrative Committee on Coordination, Subcommittee on Nutrition
ALAN	Archivos Latinoamerianos de Nutriticion
ASOTRIGO	Asociación de Trigo (Venezuelan Association for Wheat)
CAVIDEA	Consejo Venezolano Industria de Alimientos (Venezuelan Chamber of the Food Industry)
CENA	Comisión para el enriquicimento nutriciónal de los alimentos (Commission for the Nutritional Enrichment of Foods, Venezuela)
COVENIN	Comisión Venezolana de Normas Industriales (Venezuela Commission for Nutritional Standards)
DHA	Departamiento de Higiene de Alimentos (Department of Food Hygiene, Venezuela)
FUNDACREDESA	Fundación para el estudio del crecimiento naciónal y desarrrollo humano (Foundation for the Study of National Growth and Human Development, Venezuela)
IOM	Institute of Medicine, USA
INACG	International Nutritional Anemia Consultative Group
INF	International Nutrition Foundation
INH"RR”	Instituto Nacional de Higiene Rafael Rangell (National Institute of Hygiene, Venezuela)
INN	Instituto Nacional de Nutrición (National Institute of Nutrition, Venezuela)
IDPAS	Iron Deficiency Program Advisory Service
IVIC	Instituto Venezolano de Investigacións Cientificas (Venezuelan Institute for Scientific Investigation)
MI	Micronutrient Initiative
MSPS	Ministerio de Salud y Promoción Social (Ministry of Health and Social Development, Venezuela)
NAS	National Academy of Science, USA
NU	Nutrition Units (of INN in each province)
PAHO	Pan American Health Organization
PAMM	Program Against Micronutrient Malnutrition
SISVAN	Systema de Vigilancia Alimentaria Nutriciónal (Nutritional Surveillance System of INN, Venezuela)
UNICEF	United Nations Children's Fund
UNU	United Nations University
VENMAIZ	Asociacion Venzolana de Industriales de Harina de Maíz (Venezuelan Industry Association for Wheat Flour)
WHO	World Health Organization

APPENDIX I

PREVALENCE AND CONSEQUENCES OF MICRONUTRIENT DEFICIENCIES

1. POPULATION AFFECTED BY NUTRIENT DEFICIENCIES

The numbers and proportion of the world's population suffering from micronutrient deficiencies are staggering.

IRON

WHO estimates suggest that 2 billion people suffer from iron deficiency and iron deficiency anemia, one-third of the world's population. The prevalence figures for iron deficiency and iron deficiency anemia in women and children are particularly striking. Table 1 gives a breakdown of the numbers affected by iron deficiency by region and the percentage of pregnant women with anemia.

Table 1. NUMBER OF IRON DEFICIENT PERSONS (WHO)

WHO REGION	ANEMIC OR IRON DEFICIENT (millions)	PREVALENCE OF ANEMIA IN PREGNANCY (%)
AFRICAN	206	52
AMERICAN	94	60
EUROPEAN	27	18
E. MEDITERRANEAN	149	50
SOUTHEAST ASIAN	616	74
WESTERN PACIFIC	1058	40
DEVELOPED		18
DEVELOPING		56
TOTAL	2150	51

Pregnancy anemia rates are in excess of 40% in all developing regions. Even in industrialized countries iron deficiency remains a public health problem. It is estimated that individuals with iron deficiency are approximately double those with frank iron deficiency anemia (Hallberg et al. 1997). Thus 80 to 100% of individuals in vulnerable groups in developing countries are biologically deficient in iron. This is a powerful argument for iron fortification of cereal staples in all developing countries provided that its effectiveness can be established.

IODINE

While the numbers of persons at risk from iodine deficiency is dropping with successful international efforts to extend the iodation of salt, an estimated 200 million women of childbearing age are still at risk worldwide. As certified by WHO/UNICEF, Venezuela has eliminated this deficiency as a public health problem by the universal iodation of salt, but experience elsewhere indicates that a salt iodation program must be continuously monitored and sustained.

VITAMIN A

The global problem of vitamin A deficiency is also diminishing as a result of dietary improvement and vigorous promotion of intervention programs by the international agencies, but an estimated 200 million children are probably at risk of increased mortality as a result of subclinical vitamin A deficiency. As in most developing countries there is evidence of subclinical vitamin A deficiency of public health significance in Venezuela. In a study of preschool children of low income families in Valencia, Carabobo State 6.1% were deficient (<20 µg/dl serum retinol) and 26.8% marginally so (20-30 µg dl serum retinol) (Solano et al. 1997, 1998).

OTHER MICRONUTRIENTS

While the prevalence of folic acid deficiency is unknown, there is sufficient concern that the United States has approved the addition of folic acid to the fortificant mix for cereal flours, and other countries with fortification programs are rapidly adopting this measure. Information on the global prevalence of other vitamin deficiencies is also limited and mostly based on an analysis of dietary intakes. However, there are hundreds of population specific studies in developing countries whose findings suggest that deficiencies of riboflavin, vitamin B12, pyridoxine, and thiamin are common. There are also an increasing number of studies reporting zinc deficiency in some populations.

2. FUNCTIONAL CONSEQUENCES OF MICRONUTRIENT DEFICIENCIES

IRON

While approximately 73% of the body's iron is normally incorporated into hemoglobin and 12% in storage complexes, a very important 15% is incorporated into a wide variety of other iron-containing compounds, many of them enzymes of vital importance to normal function. With frank anemia these effects are more severe and general weakness is observed. The functional consequences of iron deficiency are diverse and potentially crippling.

Iron deficiency early impairs a variety of immune responses that are important for resistance to infections including lymphocyte phagocytic capacity, complement fraction C-3, lymphocyte response to mitogenic stimuli and numbers of T-cells (CD-4, CD-9, CD-12) (Srikantia et al. 1976, Chandra and Newberne 1977, Scrimshaw and SanGiovanni 1997). With iron supplementation morbidity decreases (Basta et al. 1979, Husaini et al. 1981, Hussein et al. 1989).

The infant brain that was developing rapidly during the latter part of pregnancy continues to do so throughout infancy. Iron deficiency anemia during this period can result in a downward shift in the distribution of cognitive test scores that becomes permanent (Polliitt et al. 1989, Lozoff et al. 1998, Scrimshaw 1998). Iron deficiency anemia affects cognitive performance adversely at any age but is reversible to the extent that it is not associated with iron deficiency in infancy (Beard et al. 1995, Brunner et al. 1986).

Studies in many countries (Hallberg and Scrimshaw 1983, Vijayalaksmi et al. 1987, Scrimshaw 1990) confirm a sharp drop in physical capacity proportional to hemoglobin level as measured by treadmill tests (Viteri 1976, Spurr et al. 1973, Gardner et al. 1977) and productivity of rubber tappers (Basta et al. 1979) and tea-pickers (Edgerton et al. 1981, Husaini et al. 1981). When iron is given, the reduced muscle strength associated with anemia recovers well before there is any hemoglobin response to treatment, suggesting that it is due to impaired iron-dependent enzymes in muscle.

Studies in Venezuela have demonstrated that individuals with severe iron deficiency anemia lose their capacity to maintain normal body temperature when exposed to moderate cold. They also identified the biological mechanism involved (Martínez-Torres et al. 1991).

Iron deficiency anemia during pregnancy is dangerous for the mother because it leads to poorer pregnancy outcomes and increases her risk of morbidity and mortality. Equally or more important is that it decreases the iron stores of the infant at birth (Milman et al. 1999, Blot 1999, Allen 2000). These are essential to supplement the iron in breastmilk until complementary foods that supply iron are appropriately introduced.

Infants born of iron deficient mothers risk early iron deficiency anemia and its cognitive consequences. Infants of low birth weight have even lower iron stores and may need additional iron as early as two months to avoid brain damage (UNICEF/UNU/WHO/MI 1999). In some studies iron deficiency has been associated with poor child growth (Pollitt et al. 1985, Scrimshaw 1990).

IODINE

The more severe manifestations of iodine deficiency, exemplified by the feeble-minded cretinous dwarfs, are rare. Endemic goiter in the latter part of pregnancy when the brain is growing rapidly is associated with the same kind of shift to the left in cognitive capacity (I.Q.) described above for iron deficiency in infancy (Stanbury 1994). This effect also is largely irreversible after birth.

B VITAMINS

A third micronutrient deficiency that can have serious neurological consequences is that of folic acid in the first few weeks of pregnancy when the central nervous system is forming. The deficiency results in an increase in the frequency of neural tube defects such as hydramnious and spina bifida (Daly et al. 1997). By the time the pregnancy is recognized it is usually too late for supplementation to be effective. This is a strong argument for including folic acid in the enrichment mix used for cereal flour fortification (Shaller and Olson, 1996, Cuskelly et al. 1999). There is recent confirmation that the addition of folic acid to the fortification of cereal flours in the United States has been successful in raising blood levels of this vitamin (Chumenkovitch et al. 2001, Caudill et al. 2001).

Deficiencies of folic acid, vitamin B12, and pyridoxine lead to a buildup of the amino acid homocysteine in the blood that is an independent risk factor for atherosclerosis and ischemic heart disease (Boushey et al. 1995, Tucker et al. 1996, Jaques et al. 1999). This is an additional reason for requiring the fortification of cereal flours with folic acid. Moreover, deficiencies of this nutrient and of vitamin B12 are a cause of anemia independent of iron deficiency.

Riboflavin and niacin deficiencies lead to skin lesions and if severe to immune deficits (Scrimshaw and San Giovanni 1997). Vitamin B-12 and thiamin deficiencies can lead to peripheral nerve damage. The classical nutritional diseases of beri-beri and pellagra are due to a deficiency of thiamin and niacin, respectively. Deficiencies of folic acid or vitamin B12 are a cause of anemia independent of iron deficiency. In the elderly, borderline or deficient B-vitamin status have been reversibly associated with impaired cognition and memory.

VITAMIN A

Vitamin A deficiency in infancy and early childhood was once a common cause of the eye disorders of xeropthalmia and keratomalacia often resulting in blindness (McLaren and Frigg 2001). Fortunately, these are no longer of major concern in most developing countries except among refugees and persons displaced who no longer have their usual access to food because of war, civil disturbances, and natural disasters. However, there is concern for the effect of widespread subclinical vitamin A deficiency on deaths of preschool children.

In eight large-scale vitamin A supplementation studies preschool mortality was reduced from 20% in Ghana to 50% in Tamil Nadu. Results of the supplementation were intermediate in Aceh, Indonesia, Sarlahi, Nepal, and Ghana (Beaton et al. 1993, Martorell et al. 1998). For reasons that are not clear, there was no significant decrease in mortality in the studies in Somalia and Hyderabad, India although it is speculated that other nutritional factors may have been limiting. The average reduction in the eight studies was 23%.

3. WHY DEFICIENCIES WITH SUCH SERIOUS CONSEQUENCES ARE SO LITTLE RECOGNIZED

None of these micronutrient deficiencies is evident from symptoms that the victim identifies with a nutritional deficiency or with their diet. All require diagnostic data that must be interpreted by a knowledgeable health professional. Unfortunately many health professionals are not fully aware of the consequences even when they can identify the deficiency.

For these reasons fortification and other programs to control micronutrient deficiencies need to be supported by a convincing body of scientific evidence and strong advocacy efforts. Without such evidence and leadership, populations will continue to suffer even though a measure as feasible and cost effective as fortification of staple foods could significantly improve the health, developmental potential, and productivity of many national populations.

APPENDIX 2

WHY IRON DEFICIENCY PREVENTION HAS LAGGED SO FAR BEHIND THAT OF IODINE AND VITAMIN A

The reasons that can be identified for the comparatively slow progress and limited efforts to overcome iron deficiency, despite its magnitude and consequences, include some controversial technical issues and some largely unfounded concerns. The consensus report of the field-oriented, science-based technical workshop, sponsored by UNICEF, WHO, UNU, and MI (1999) strongly emphasized that none of these reasons is any longer an excuse for the failure to give the prevention of iron deficiency the highest nutrition priority for most developing country populations; so did the IOM report on *Prevention of micronutrient deficiencies. Tools for policy makers and public health workers* (Howson et al. 1998).

One of the strongest reasons why less effort has been devoted to the prevention of iron deficiency is that it has received less effective global leadership and advocacy efforts than either iodine or vitamin A deficiencies. This is due in part to a perception that it is more difficult and complex to prevent. The Venezuelan initiative stands as a notable exception. The technical workshop emphasized the clear evidence that simple, inexpensive tools and methods for feasible, sustainable, and effective low-cost interventions are available and gave the highest priority to fortification of basic food staples.

A reason sometimes given for delaying iron intervention programs in populations with a high prevalence of anemia is that deficiencies of folic acid, vitamin B12, and less commonly of other vitamins and minerals, can also cause anemia. However, experience worldwide confirms that when anemia prevalence rates rise above 10%, the main cause is iron deficiency, either because of the low availability of dietary iron, iron losses due to parasites, or both. Anemia would not be such a public health problem in many populations if it were not for iron losses due to hookworm and to Shistosomiasis. The additional nutrients supplied by the multiple micronutrient fortification of wheat flour may contribute to a further decrease in anemia that may be due to causes other than iron.

Another doubt is that iron fortification may not be effective in individuals with sickle cell disease, thalasemia and other genetic hemoglobinopathies that can increase iron needs. However, field experience indicates that these conditions also respond to iron administration (UNICEF/UNU/WHO/MI 1999). Clinicians in some countries have delayed fortification programs by publicly expressing concern that they could exacerbate hemochromatosis in individuals homozygous for this genetic disease. Yet this condition occurs in only 0.25% of populations of Celtic decent, and is rare or nonexistent in individuals not originating in northern Europe. No cases have been found in the African Countries studied (Algeria, Ethiopia, and Senegal). It has never been reported from Venezuela.

There has been a hesitance to provide iron interventions to populations in which malaria is endemic even though they are often severely anemic. Recent WHO studies confirmed that malaria is an independent risk factor for anemia in these populations that usually are also iron deficient. Giving iron to individuals with malaria has no adverse impact of public health concern. (Gillespie 1998, INACG 1998). Instead populations with endemic malaria are also usually iron deficient and need iron fortification programs as well as malaria control to reduce the burden of anemia.

The claim that iron administration in preventive doses, and especially the levels achieved with fortification, could increase the frequency or severity of infections is based on a misunderstanding of the data. Withholding iron from infectious agents is an important biological mechanism of resistance to infections (Rogers 1974, Weinberg 1977). In the severely iron-deficient host and in children with kwashiorkor cell mediated immunity and leukocyte function are greatly reduced. Under these circumstances, giving parenteral iron has been associated with mortality from overwhelming infection (McFarlane et al.1970, Murray et al. 1978). This is because the invading organism is supplied with iron beyond the body's capacity to withhold iron at a time when immune defenses are greatly weakened.

It has sometimes been difficult to convince some local clinicians that these very special circumstances are not relevant to much needed programs to reduce or prevent iron deficiency and that they will not exacerbate infections (Scrimshaw 1990, UNICEF/UNU/WHO/MI 1999). On the contrary successful fortification with iron can be expected to decrease morbidity and mortality from infections.

Another argument sometimes given as a reason not to accept iron fortification is the claim that it could increase prevalence rates of coronary heart disease and cancer. A U.S. National Academy of Sciences overview concludes that there is currently no epidemiological evidence to support this hypothesis (National Research Council 1995). They stated that there is no valid evidence for a significant role of iron intake, whether by diet or other routes, in the etiology of the diseases.

APPENDIX 3.   REACHING GROUPS WITH SPECIAL NEEDS

1. PREGNANT WOMEN

Women commonly enter pregnancy with anemia, and it is exacerbated by the demands of pregnancy and by physiological hemodilution. Current WHO/UNICEF policy calls for the administration of daily iron and folic acid supplements during pregnancy in populations where anemia is endemic. Unfortunately, women rarely come for prenatal care early enough for the folic acid to prevent neural tube damage during the crucial initial weeks of organ formation immediately after conception.

The time to prevent folate deficiency is before the mother becomes pregnant. This is also true for iron because supplementation of a mother with moderate to severe anemia after her pregnancy is recognized is too late to correct iron status although this action may prevent it from getting worse. It is for this reason that all women of childbearing age receive special benefits from multinutrient cereal fortification. It helps to ensure a more satisfactory micronutrient status before conception.

2. INFANTS

The 1999 survey of FUNDACREDESA found 70% of Venezuelan children under one year of age to have serious deficiencies of iron (serum ferritin less than 12 µg/L) and a high prevalence of anemia (plasma hemoglobin less than 12 g/dl. As noted above, iron is essential for the development of the infant brain and the distribution of cognitive capacity is shifted downward in a deficient population. This is not reversed by later improvement of iron status (UNICEF/UNU/WHO/MI 1999).

The iron in breast milk is highly available and sufficient to complement the iron stores of infants born at term from well-nourished mothers until approximately six months. However, if the mother is iron deficient during pregnancy, the iron stores of her child at birth are reduced and an iron source complementary to breast milk may be needed earlier to avoid anemia developing. (Allen 2000). The iron stores of low birthweight babies may be depleted by 2 to 4 months and they develop anemia at this early age. For these reasons, it is desirable to bring children to the health center around four months for evaluation of their hemoglobin status and determination of their need for additional iron at this time. After six months all children should received iron from a source that complements breastmilk.

Unfortunately children less than two years of age do not benefit significantly from fortified staple foods. At the rate of fortification acceptable and safe for the overall population, the amounts of iron that they receive are too small to be effective. In countries where use of processed cereals designed specifically for infants are commonly used, the higher levels of iron in these products provide needed daily requirements. Dietary guidelines often state simply “feed complementary foods rich in iron and other micronutrients” to young children. However, for poor families there are few common, affordable foods or meals that will result in the infant receiving sufficient bioavailable iron to meet requirements even when breastfeeding continues.

It is internationally recommended that in populations in which fortified cereals are unavailable or prohibitively expensive for the poor, iron supplementation is needed by six months of age even for full term, normal birthweight breastfed children (Stoltzfus and Dreyfus 1998). While conventional industrially processed fortified cereals can meet the micronutrient needs of children in families that are economically better off, this approach cannot be relied upon for the majority of developing country children in this age group.

An exception to this is the development of low cost vegetable mixtures. INCAPARINA in Guatemala is nutritionally more complete than milk and is stilling selling at one-fifth the cost of milk even after forty years (Barenbam et al. 2001). Every country needs fortified weaning foods that are low cost because they use local vegetable components. Issues of distribution and compliance remain major challenges and work remains to provide an effective, safe and affordable supplement.

It is important to discuss with the pharmaceutical industry the need for soluble iron compounds that are affordable and convenient to administer. They should be available for purchase by government and private agencies and especially should be accessible to persons whose economic resources are very limited. It will be important to involve actively the cooperation of parents in a measure that affects the future intellectual capacity of their children.

Regardless of the method chosen, parents should be advised not to give food or fluids other than breast milk until about six months of age. Thereafter, complementary foods supplying iron should be given or an iron supplement should be provided. However, if the mother was iron deficient or the child was born with low birthweight, supplementary liquid or solid iron in suitable form may be needed by four months of age, and even earlier in the case of low birthweight babies.

Other measures that can reduce the risk of iron deficiency in early infancy are the promotion of birth spacing and the delayed clamping of the umbilical cord. A number of studies have demonstrated that allowing the cord to stop pulsating before it is clamped and tied, about one minute, gives the baby an infusion of iron whose benefits can be detected in the infant for at least six months (Grajeda et al. 1997). It is important that at six months children be brought to the clinic or health center for evaluation of their hemoglobin and determination of their need for further measures.

The fact that for older infants and younger preschool children the need for additional iron is not met by cereal flour fortification with iron does not in any way detract from the value of the fortification program. The advantage of fortification of cereal flours is that it reduces the degree of iron deficiency of the mother before pregnancy even if it is not sufficient to fully correct it. Moreover, it does benefit children from two years of age onward. For children over two years of age the prevalence of iron deficiency decreased from 37% in 1993 to 15% in 1994. The corresponding drop in anemia in this period was from 19% to 9 % (Layrisse et al. 1996).