

## Complementary Food Supplements to Achieve Micronutrient Adequacy for Infants and Young Children

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### ABSTRACT

Many children in developing countries survive on a nutritionally inadequate diet. Dietary inadequacies during the complementary feeding period can be prevented by using complementary food supplements (CFSs) such as water dispersible or crushable micronutrient tablets, micronutrient sprinkles added to food just before feeding, or fortified spreads added to food just before feeding or fed as a snacks. A meeting was convened to discuss technical and operational issues related to the development of these new approaches and to identify knowledge gaps. The technical issues covered: what micronutrients to include, tolerable upper intake limits, bioavailability, micronutrient and macronutrient stability, package systems and amounts, encapsulation technologies, methods to limit or eliminate allergens, bacterial and chemical contamination, interactions between CFSs and complementary foods, and flavoring agents. Operational issues included: identifying the market positioning of CFSs, cost positioning of CFSs, regulatory requirements,

CFS production and technology transfer, quality assurance, and public-private sector partnership and coordination. Intervention trials are needed to determine the efficacy of CFSs in preventing micronutrient deficiencies. Other important knowledge gaps relate to technical and operational issues. Sprinkles and tablets are produced using well-known technologies, but further research is needed to modify them for use as CFSs. Spread development is not as advanced as sprinkle and tablet development, and further research is needed to improve the technology. Although none of the products is ready for widespread use, enough information is available to set research priorities and accelerate product development and implementation. **JPGN 36:316–328, 2003. Key Words:** Complementary food supplements—Developing countries—Micronutrient sprinkles—Micronutrient spreads—Water dispersible micronutrient tablets—Crushable micronutrient tablets. © 2003 Lippincott Williams & Wilkins, Inc.

### BACKGROUND

In most developing countries the prevalence of undernutrition and micronutrient deficiencies is high among infants and young children aged 6 to 23 months (1). Ideally, all children in this age range are breast fed. As they get older the energy and nutrient contribution from complementary food becomes increasingly important for meeting daily requirements. For many infants and young children, however, the small quantities of cereal-based porridges commonly fed to them do not contain enough

energy and micronutrients to meet daily requirements. The generally accepted recommendations for improving the nutritional status of children in this age group are to feed children locally available micronutrient-rich foods and to encourage local production of low-cost, industrially processed, fortified cereal-based complementary foods. Increasingly, however, both approaches are recognized as having limitations. A nutritionally adequate complementary diet with locally available food requires the use of animal source foods (2,3) that are expensive and beyond the reach of many households. Processed, fortified complementary foods, such as the United Nations Children's Fund (UNICEF) UNIMIX or the U.S. PL480 Corn Soy Blend, are even more expensive than traditional local complementary foods and are invariably very different from the traditional diet, which affects their acceptability. Even when local food companies market a fortified complementary food, the cost is gen-

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erally beyond the reach of many except the wealthiest people, whose infants and young children are not those most at risk of undernutrition.

New approaches for preventing dietary inadequacies during the complementary feeding period were recently proposed. These approaches include water-dispersible or crushable micronutrient tablets (4) or micronutrient sprinkles (5) that are added to food just before feeding and fortified spreads that can be added to food just before feeding or fed as a snack (6). These products can be considered as complementary food supplements (CFSs) (i.e., intended to supplement complementary foods to meet the nutritional needs of older infants and young children). All three products have been designed to provide one or two recommended dietary allowances (RDAs) of vitamins and minerals in a small volume at a low cost. They are also assumed to be relatively easy to integrate into existing food practices because the objective is simply to add a component that delivers the micronutrients that are either missing or present in inadequate amounts in the usual diet rather than to change feeding practices. Another advantage of a CFS is that it can provide an appropriate amount of nutrients for each child regardless of how much complementary food is consumed. This is important because intakes of processed complementary foods range ten-fold depending on age and breast milk intake (2), and the fortification level may not be appropriate for such a wide range of intakes.

The proposed CFSs differ sharply from each other in their formulation and characteristics (Table 1): tablets are a pharmaceutical form, fortified spreads are a food, and sprinkles are midway between these two products.

The potential use of the new technologies in developing countries is attracting considerable interest. For this reason the United States Agency for International Development and the Institut National de la Santé et de la Recherche Médicale convened a group of food scientists and technologists in Paris (the Boussingault meeting) on July 9–10, 2002, to discuss technical and operational issues related to the development of these promising new approaches and to identify knowledge gaps. No attempt was made to recommend one approach over the other or to discuss distribution mechanisms, because all products are still under development and recommendations would be premature. Moreover, the most feasible approach may differ from one country to another or even within a country as a result of several factors, including feeding practices, distribution channels, and cultural and economic factors. The following sections briefly describe each product followed by the issues discussed during the meeting.

**Dispersible or Crushable Tablets**

In 1999, UNICEF recommended that a micronutrient supplement containing one or two times the RDAs of 10 vitamins and 4 minerals be developed and field tested. The term *foodlet* was coined to describe this approach as being midway between a pharmaceutical product and a food supplement (4). The low-cost, stable, readily crushable and water-dispersible tablets developed can be mixed with food or chewed directly. The advantage of this formulation is that users may perceive adding the crushed tablet to food to be a more food-based rather than a medical intervention, which usually has a low

**TABLE 1.** Comparison of possible complementary food supplements

	UNICEF crushable tablets	WHO dissolvable tablets	Sprinkles	Spread
Encapsulation	Not needed	Not needed	Needed	Iron encapsulation may be needed to extend shelf-life
Excipient	None	Cellulose or dextrin	Dextrin	Food products: powdered products such as milk products, sugar, dextrin maltose, soy flour with low melting point vegetable fat (at least 30%)
Micronutrient composition	Vitamin A: 375 µg Vitamin D: 5 µg Vitamin E: 6 IU Vitamin B <sub>1</sub> : 0.5 mg Vitamin B <sub>2</sub> : 0.5 mg Vitamin B <sub>6</sub> : 0.5 mg Vitamin B <sub>12</sub> : 0.9 µg Vitamin C: 35 mg Folic acid: 150 µg Niacin: 6 mg Iron: 10 mg Zinc: 10 mg Copper: 0.6 mg Iodine: 50 µg	Folic acid: 50 µg Iron: 10 mg Zinc: 10 mg	Vitamin A: 300 µg Vitamin C: 50 mg Folic acid: 150 µg Iron: 30 mg Zinc: 5 mg	Flexible. One to two RDAs of iron, zinc, and all vitamins can be incorporated into 10 to 100 g of spread
Can be consumed separately	As a pharmaceutical	Yes	No	Yes

compliance in preventive applications. Side effects, in particular stomach irritation, are also likely to be lower if tablets are mixed with food, although this may reduce iron and zinc absorption.

The foodlet was developed and used in a multicenter supplementation trial in infants and young children in Peru, Indonesia, Vietnam, and South Africa but the results are not yet available (Rainer Gross, UNICEF New York, personal communication, 2002). Three of the four studies, however, administered the foodlet as a stand-alone product rather than as a CFS.

A second dispersible tablet containing iron, zinc, and folate was developed for the ongoing World Health Organization (WHO)/United States Agency for International Development's (USAID) multicenter study in India, Nepal, and Zanzibar. In principle, other micronutrients could also be added. These tablets are easily and quickly dissolved in water or breast milk. They were developed for administration as a stand-alone product rather than as a CFS. Aspartame and vanilla flavoring mask the metallic aftertaste of the minerals.

### Sprinkles

Sprinkles are a vitamin and mineral mix packaged in small sachets containing a daily dose of micronutrients designed to be mixed with food. Sprinkles containing iron, vitamin A, zinc, and vitamin C (as an absorption enhancer rather than for nutritional purposes) have been shown to be efficacious in treating anemia in Ghana (7). Other micronutrients can also be added. To avoid sensory problems, iron is encapsulated with a thin coating of a soy-based hydrogenated lipid. The sprinkle sachets contain bland-tasting filler comprised of edible carbohydrate, which adds volume to the micronutrients so they can be easily handled. Caretakers are instructed to sprinkle the entire contents of the sachet on the infant's gruel or porridge just before feeding.

### Spreads

Fortified spread is used in therapeutic feeding to treat severely undernourished children in relief operations (8). It is prepared by mixing dry powdered ingredients (i.e., dried milk products, precooked soy flour, sugars, maltodextrin, minerals, and vitamins) with a vegetable fat such as peanut butter. The viscosity and melting point of the fat must be such that the resulting product is easy to store and swallow. Spreads are made without water and thus they can be safely stored at home without any risk of pathogenic bacterial proliferation.

The spread used in therapeutic feeding is well accepted by undernourished children, suggesting that a similar product could be designed as a CFS for preventive purposes. Because a strong flavored fat base—such as peanut—is used, the metallic taste of soluble minerals

can be masked more easily than in other products. In therapeutic settings, older children usually eat the spread as a snack. It could also be consumed as a snack when used as a CFS, but because infants aged 6 to 12 months may have difficulty swallowing a thick paste, mixing it into traditional porridges just before serving may be more appropriate.

The spread formulation is flexible, and the amount of spread needed to deliver a daily dose of micronutrients can vary from 10 g/d to 100 g/d. The energy content of spreads is 22 kJ/g (5.4 kcal/g); thus an intake between 10 g/d and 100 g/d provides 220–2200 kJ/d (54–540 kcal/d), which can be a significant boost to the energy density of the complementary food that may be needed in some situations.

## PRODUCT DESIGN

### Setting the Micronutrient Content of Complementary Food Supplements

Ideally, the quantity of micronutrients included in a CFS is based on the difference between the total micronutrient intake from both breast milk and complementary food and the reference dietary intake. This approach, however, is problematic because of uncertainties regarding the definition of an adequate level of intake for some nutrients for children aged 6 to 23 months and also because of variable breast milk intake levels.

In 1998, the amount of micronutrients to be provided by complementary foods was estimated by subtracting the amount of micronutrients provided by breast milk from the recommended nutrient intake (RNI) for children ages 6 to 8, 9 to 11, and 12 to 23 months (9,10). These values were then converted into desired nutrient densities (per 100 kcal of complementary food) by dividing by the amount of energy needed from complementary foods at each age (2). Since 1998, new dietary reference intakes (DRIs) have been published by the U.S. Institute of Medicine (IOM) for many micronutrients (11–14). Because of the dearth of data for children under age 2 years, most DRIs were estimated differently for children below and above age 12 months. For infants younger than 12 months, DRIs were based primarily on the adequate intake (AI; i.e., the mean observed intake of healthy individuals). For infants aged 7 to 12 months the AI values were calculated from the estimated intake from breast milk added to the amount expected to be ingested from complementary foods. For children aged 12 to 23 months, most DRIs were based on DRI values extrapolated from adults or older children. As a result, some inconsistencies exist between the DRIs for children aged 7 to 12 and 12 to 23 months, in particular for vitamins A and C, folic acid, calcium, and phosphorus.

WHO and the Food and Agriculture Organization of the United Nations (FAO) recently updated their report

on recommended nutrient intakes (15), which are most relevant to developing countries. Because of the differences in the estimates of micronutrient requirements as well as changes in energy requirements since 1998, the desired nutrient density of complementary food (micronutrient content per 100 kcal of food) depends on which set of values is used: WHO 1998, IOM DRIs, or WHO/FAO 2000 (Table 2). The differences in desired nutrient density are particularly apparent for vitamin A, calcium, zinc, thiamin, folate, and vitamin C.

Although there is uncertainty about which set of RNIs to use for defining the optimal nutrient composition of complementary foods, several micronutrients would be considered to be problem nutrients regardless of the requirement values chosen. Problem nutrients are identified by comparing estimates for the desirable nutrient density of complementary foods with the actual densities of the nutrients in the foods consumed by breast-fed children. These data are available for children aged 6 to 23 months in Bangladesh, Guatemala, Ghana, Mexico, Peru, and the United States (16). They suggest that iron, zinc, and vitamin B6 are problem nutrients in all of these developing countries whereas riboflavin and niacin are

problem nutrients in only some of these developing countries. Even in the United States, iron and zinc are problem nutrients in the first year of life despite the widespread availability of iron-fortified foods. The situation for calcium, vitamin A, thiamin, folate, and vitamin C depends on which desired levels are deemed most appropriate. If the new WHO/FAO requirements are used, for example, folate, thiamin, and calcium would be considered problem nutrients in many developing countries and vitamins A and C would be considered problem nutrients in some developing countries (Table 2 shows the data for infants 6–11 months). Despite these discrepancies, the picture emerging from these data is that multiple micronutrients are likely to be limiting in the diets of children in developing countries between ages 6 and 23 months.

In choosing the micronutrients to include in a CFS, the probability of deficiency in the population must be considered. Priority must be given to deficiencies that are documented by biologic or clinical data. Nutrients with moderate probability of deficiency can be included provided their tolerable upper intake level is considerably higher than the usual intakes and their cost is low com-

**TABLE 2.** Nutrient densities (per 100 kcal) of diets of infants ages 6–8 and 9–11 mo in Bangladesh, Ghana, Guatemala, Peru, and the United States compared with the desired average nutrient density

	Average desired nutrient density: based on			Median density (per 100 kcal) (16)				
	WHO (2)	IOM (11–14) DRIs	WHO/FAO (15)	Bangladesh	Ghana	Guatemala	Peru	United States
<b>6–8 mo</b>								
Number of children				50	207	194	107	36
Protein (g)	0.7	1.0	1.0	1.9	3.3	2.2	2.6	2.6
Vitamin A (µg RE)	5	81	31	<b>0</b>	<b>7</b>	87	35	95
Calcium (mg)	125	40	105	<b>16</b>	<b>35</b>	<b>27</b>	<b>19</b>	<b>67</b>
Iron (mg)	4.0 <sup>a</sup>	5.3 <sup>a</sup>	4.5	<b>0.4</b>	<b>1.2</b>	<b>0.5</b>	<b>0.4</b>	<b>3.6</b>
Zinc (mg)	0.8	1.1	1.6	<b>0.2</b>	<b>0.6</b>	<b>0.4</b>	<b>0.4</b>	<b>0.4</b>
Riboflavin (mg)	0.07	0.08	0.08	<b>0.04</b>	<b>0.03</b>	<b>0.06</b>	<b>0.07</b>	0.18
Thiamin (mg)	0.04	0.08	0.08	<b>0.04</b>	<b>0.07</b>	<b>0.04</b>	<b>0.04</b>	0.14
Niacin (mg) <sup>b</sup>	1.1	1.5	1.5	<b>0.9</b>	<b>0.8</b>	<b>0.4</b>	<b>0.5</b>	1.5
Niacin equiv. (mg)				<b>1.3</b>	<b>1.3</b>	<b>0.8</b>	<b>1.0</b>	
Folate (µg)	0	11	11	<b>5</b>	—	7	—	—
Vitamin B <sub>6</sub> (mg)	0.09 <sup>c</sup>	0.12	0.12	<b>0.02</b>	—	<b>0.05</b>	—	<b>0.10</b>
Vitamin C (mg)	0	11	1.5	<b>0</b>	<b>0.02</b>	2.3	2.3	7.2
<b>9–11 mo</b>								
Number of children				<b>66</b>	<b>171</b>	148	99	31
Protein (g)	0.7	1	1	<b>2.5</b>	<b>3.1</b>	2.7	2.6	3.4
Vitamin A (µg RE)	9	63	30	<b>1</b>	<b>9</b>	62	29	88
Calcium (mg)	78	32	74	<b>20</b>	<b>40</b>	37	27	53
Iron (mg)	2.4 <sup>a</sup>	3.5 <sup>a</sup>	3	<b>0.4</b>	<b>1.3</b>	0.6	0.4	1.2
Zinc (mg)	0.5	0.7	1.1	<b>0.3</b>	<b>0.6</b>	0.4	0.4	0.4
Riboflavin (mg)	0.04	0.06	0.06	<b>0.05</b>	<b>0.02</b>	0.06	0.07	0.08
Thiamin (mg)	0.04	0.06	0.06	<b>0.05</b>	<b>0.06</b>	0.05	0.04	0.1
Niacin (mg) <sup>b</sup>	0.9	1	1	<b>1.0</b>	<b>0.7</b>	0.5	0.5	1.1
Niacin equivalents (mg)				<b>1.4</b>	<b>1.2</b>	0.7	1.0	—
Folate (µg)	0	9	9	<b>8</b>	—	13	—	—
Vitamin B <sub>6</sub> (mg)	0.08 <sup>c</sup>	0.08	0.08	<b>0.03</b>	—	0.07	—	0.10
Vitamin C (mg)	0	8	1.7	<b>0.3</b>	<b>0.9</b>	2.4	1.1	6.4

**Bold type** indicates that the observed density is below at least 2 of the 3 reference values for average desired density. RE, retinol equivalents.

<sup>a</sup> Medium bioavailability of iron.

<sup>b</sup> Excluding the contribution of dietary tryptophan to niacin synthesis.

<sup>c</sup> Corrected value.

pared with the total cost of CFSs. The latter is likely to be the case for most vitamins apart from vitamin E and to a lesser extent vitamins C and A.

Ideally the amounts of micronutrients to include in a CFS will vary by age group, given that RNIs change with age and that the amount of food a young child eats increases with age. Such an approach, however, is unnecessarily complicated because intakes slightly higher than one RNI present no risk to the child. The critical issue is that the concentrations of micronutrients in CFSs result in a total daily intake of one to two RNIs for all children aged 6 to 23 months after the amounts already present in breast milk and complementary food are accounted for.

### Maximum Levels of Micronutrients to be Incorporated in Complementary Food Supplements

Few countries (United States and Canada (11–14), China (17), and Japan (18)) have officially defined Tolerable Upper Intake Levels (ULs) for micronutrients as the WHO/FAO has done (15). The European Scientific Committee on Food is currently evaluating the UL for vitamins and minerals and 13 opinions have been published by July 2002. Some countries such as Germany, Austria, Switzerland, and France have commented on safety aspects in their national recommendations without issuing specific ULs. The European Commission will be setting UL for vitamins and minerals used in food supplements based on assessed UL (risk assessment) adjusted by a risk management exercise (19). These ULs are due to come into European law by mid-2003.

Tolerable Upper Intake Levels are defined as the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals. The UL is based on one adverse health effect determined to be the most relevant for a particular nutrient. It is calculated from either the nutrient intake associated with no observed adverse health effects or the lowest nutrient intake associated with an observed adverse health effect. The additional introduction of an uncertainty factor specific for each nutrient accounts for uncertainties in data (i.e., extrapolation from animal data to humans or lack of data on chronic exposure) as well as for expected variability in response within the population (11–14). Some ULs are close to the RNIs because of the method used in their determination. ULs have been defined for healthy populations with adequate nutrient status. Their use for deficient children must be clarified for each micronutrient, but they can be used as a basis for establishing maximum levels for the nutrient content of CFSs. It is recommended that the ULs established by WHO/FAO be used as a reference (Table 3) because they are the most recent and they are based on data from other countries besides the United States. CFSs must be designed so that chronic levels of micronutrient intakes above the WHO/FAO UL will not be achieved.

**TABLE 3.** WHO vitamin and mineral intake safe upper limits for children ages 6–23 mo

Micronutrient	Toxicity/upper limit intake
Vitamin A	The smallest daily supplement associated with liver cirrhosis that has been reported is 7500 µg taken for 6 y Daily prophylactic or therapeutic doses should not exceed 900 µg/d
Vitamin D	The lowest observed adverse effect level: 50 mg/d No observed adverse effect level: 20 µg/d
Vitamin E	Appears to have very low toxicity. Evidence of prooxidant damage has been associated with feeding supplements but usually only at very high doses, e.g., >1000 mg/d
Thiamine (B <sub>1</sub> )	Toxicity is not a problem because renal clearance of the vitamin is rapid
Riboflavin (B <sub>2</sub> )	Toxicity is not a problem because of limited intestinal absorption
Niacin (B <sub>3</sub> )	Upper limit: 35 mg/d (proposed by the U.S. Food and Nutrition Board)
Pantothenate (B <sub>5</sub> )	Toxicity is not a problem as no adverse effects have been observed
Pyridoxine (B <sub>6</sub> )	Upper limit: 100 mg/d (proposed by the U.S. Food and Nutrition Board)
Vitamin B <sub>12</sub>	Intake of 1000 µg/d has never been reported to have any side effects
Folic acid	Upper limit 1000 µg/d (adapted from U.S. National Academy of Sciences)
Vitamin C	Upper limit: 1 g/d
Biotin	Toxicity is not a problem because of limited intestinal absorption
Calcium	Upper limit: 3 g/d
Iodine	The upper limit will depend on both basal status of iodine intake and age
Iron	Upper limit not provided in WHO document
Magnesium	Upper limit: 65 mg/d for children ages 1–3 y
Selenium	Upper limit: 400 µg/d
Zinc	Upper limit: 23–28 mg/d (350–430 µmol/d) for extrapolated from an adult man in relation to basic metabolic rate

Among the micronutrients, iron toxicity from excessive intake of palatable tablet-like supplements has proven fatal for young children (20,21). To limit the number of pills or capsules a small child could accidentally consume, the U.S. Food and Drug Administration recommends that products containing 30 mg or more iron per dosage unit be packaged as individual doses (e.g., in blister packages). It also recommends that an iron-containing drug or food supplements with more than 250 mg of iron per container be in child-resistant packaging (22).

### Micronutrient Stability

The stability of vitamins in a CFS depends on factors such as temperature, moisture, oxygen, light, pH, oxidizing and reducing agents, and trace minerals such as iron and copper. Vitamin A, vitamin C, and folic acid are examples of unstable vitamins. Minerals are generally stable. However, conversion of the oxidation state of iron

from ferrous to ferric could decrease bioavailability if the ferric form is insoluble.

Vitamin A (retinol) degradation is accelerated by oxygen, light, trace minerals, and low pH that can cause isomerization. In general, fatty acid esters of retinol are more stable than retinyl alone. Retinyl stability can be increased by encapsulation and by inclusion of antioxidants. Beta-carotene can also be used as a source of vitamin A but its stability and bioavailability are generally lower than retinyl and retinol esters. Furthermore,  $\beta$ -carotene is considerably more expensive than retinol.

Vitamin C is readily oxidized in aqueous systems and oxygen, low pH more so than high pH (23), and metals (copper > iron > zinc) increase its degradation. Degradation, however, can be inhibited by metal chelates such as EDTA and by encapsulation.

Folate exhibits moderate stability with degradation being accelerated with acid or alkaline pH, oxidizing and reducing agents, and light (especially in the presence of riboflavin).

Degradation of all the above vitamins is accelerated at elevated temperatures. To offset vitamin losses during food processing and storage, overages are commonly added so that the minimum desired concentration of the vitamin is maintained during the expected shelf life of the product. The amount of overage required depends on the composition and properties of the carrier system, other coexisting micro- and macronutrients, quality of the packaging, and storage conditions. In the three proposed CFSs, vitamin overages range from 20% to 30%. When an overage level is chosen, the level for each micronutrient must be set so that it does not exceed the UL and also does not incur unnecessary cost.

Nutrient stability in the existing delivery systems allows a shelf life of 18 to 24 months for dispersible tablets, 12 to 15 months for sprinkles, and 12 months for spreads. These values however, are based on current production in industrialized countries. The 12-month shelf life for spread was obtained through careful selection of primary ingredients and packaging under nitrogen. A much shorter shelf life is likely when spreads are produced locally or not packed under nitrogen. With appropriate packaging, the stability of ferrous iron has proved satisfactory in sprinkles and tablets but has yet to be determined in spreads.

#### **Micronutrient Bioavailability in Complementary Food Supplements**

For the majority of the proposed nutrients in CFSs, bioavailability is good or cannot be altered. For example, vitamin A added as retinyl acetate, retinyl palmitate, or water-soluble beadlets is typically 70% to 90% bioavailable. The sulfate, chloride, gluconate, oxide, and stearate forms of zinc are generally 20% to 40% bioavailable in cereal porridges, with zinc oxide potentially being more

poorly absorbed. Phytate may inhibit zinc absorption but this is still under investigation in children (24).

Bioavailability is a major concern for iron supplements. The bioavailability of dietary iron is generally low (2% to 20%). Moreover, the expected absorption of iron from cereal gruels in infants is 5% to 10% (25). Compounds such as phytate and some proteins decrease iron bioavailability whereas ascorbic acid and chelating compounds that maintain solubility (e.g., EDTA) increase bioavailability. Ferrous sulfate and ferrous fumarate are recommended for infant foods and have similar bioavailability (25). Other possible forms of iron include electrolytic iron, ferrous sulfate or ferrous fumarate encapsulated with hydrogenated oils, and the recently proposed micronized ferric pyrophosphate. In terms of bioavailability, the solubility of iron in the gastric juice is the most important factor. Ferrous forms of iron are more soluble than ferric forms, thus their bioavailability is often greater. Although ferric iron forms insoluble precipitates in the upper gastrointestinal tract more readily than ferrous iron, soluble ferric compounds such as ferric ammonium citrate are as well absorbed as ferrous sulfate, and ferric iron EDTA can be 2 to 3 times better absorbed than ferrous sulfate from foods containing phytic acid. Micronized ferric pyrophosphate with a particle size of 0.5  $\mu\text{m}$  is as well absorbed as ferrous sulfate (R.H. Hurrell, unpublished data, 2002). Its cost, however, is too high to make it a feasible alternative to existing forms of iron fortificants. Among the elemental forms of iron (i.e., hydrogen reduced, carbonyl, electrolytic, and the more recently available atomized irons), only electrolytic iron appears to be adequately absorbed at 50% of that of ferrous sulfate (26). Sodium ferric EDTA would be an advantageous alternative for incorporation into a CFS because it is well absorbed even in the presence of phytate in the food and has lower reactivity with fat and vitamins. So far, however, it has not been used in infant foods because international regulations prohibit its use in these foods.

All three CFSs use ferrous iron: sulfate in the spread and tablets and fumarate in the sprinkles. There is no technical obstacle to using ferrous sulfate in the sprinkles. Adding ascorbate at molar ratios of 2.0–4.0:1 (ascorbate to iron) is recommended to improve iron bioavailability (25).

The oxidation state of iron can be important for iron to promote oxidative reactions. Ferrous iron is 10 to 1000 times more pro-oxidative than ferric iron, depending on various factors, especially the pH. Given this, soluble ferric salts may present a more desirable form for use in spreads.

#### **Macronutrients in Complementary Food Supplements**

All three CFSs contain macronutrients that act as bulking agents and protection systems; in spreads they also

act as sources of macronutrients. Macronutrients are present only in small quantities in sprinkles and tablets, mainly as carbohydrates. The choice of carbohydrate will affect the flow characteristics of the premix and tablet integrity. Because vitamin stability can be decreased by the presence of moisture, choosing a low-moisture carbohydrate base for the tablets and sprinkles—such as maltodextrin or cellulose—is important. Starch is not suitable because of its high moisture content of 11% to 13%. Ideally, the carrier should have a water activity of 0.4 or less.

Spreads contain high levels of macronutrients, among which lipids play a major role in product texture. The lipid's fatty acid composition has an important role in sensory acceptability. The melting properties of fats depend on fatty acid composition, with increasing levels of unsaturation decreasing the melting point. Solid fats exist in a crystalline matrix that melts with increasing temperature. A high-melting fat should be chosen to prevent separation of components during storage at ambient temperatures. However, if the fat melts at too high a temperature, it will not melt at body temperature and will result in an objectionable mouth-feel.

High concentrations of unsaturated fatty acids in a spread may be nutritionally desirable but may cause problems with oxidative rancidity. Unsaturated fatty acids are susceptible to oxidative reaction especially in the presence of transition metals such as copper and iron. Oxidative reactions lead to the formation of rancid off-flavors and the destruction of vitamins. The latter can occur at an early stage, before fat oxidation becomes apparent. Lipid oxidation increases dramatically with increasing number of double bonds in a fatty acid. This means that monounsaturated fatty acids exhibit a much higher oxidative stability than polyunsaturated fatty acids. Because the lipids in spreads will be sensitive to oxidation when iron is included as a fortificant, it is important to limit the concentrations of polyunsaturated fatty acids. The fats currently being added to spreads are totally hydrogenated palm kernel oil, which contains no *trans* fatty acids, and rapeseed oil—a monounsaturated fatty acid. The former aids in the formation of a crystalline network and the latter provides the minimum level of unsaturated fatty acids to minimize the risk of oxidation. A balance of saturated fatty acids similar to that described above should be sought when spread formulation is altered to adapt to production conditions (i.e., locally available fats and oils and local feeding practices).

The oxidative stability of the fatty acids and nutrients in the spreads can also be improved by the addition of antioxidants. Butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are highly effective antioxidants, but their use is not allowed under current regulations for foods for infants and children (27,28). Tocopherols (vitamin E and related isomers; tocopherol esters do not have antioxidant properties) and L-ascorbyl

palmitate are antioxidants permitted in infant foods and could be used in spreads. Citric acid may also decrease oxidation as a result of its ability to chelate pro-oxidative metals. The optimal combination of different antioxidants and their effect on mineral absorption is to be established.

The proteins present in the spread can also function as antioxidants through their ability to chelate metals and inactivate free radicals. These proteins may also affect iron bioavailability. For example, casein decreases whereas whey proteins have no effect on iron absorption. Phytic acid-containing proteins such as soy and groundnut will also reduce iron and zinc bioavailability. In addition to their antioxidant properties, proteins are likely to play a role in texture through their ability to emulsify fat. If local protein sources are used in the production of spreads, their effect on lipid oxidation, iron bioavailability, and texture should be considered.

### Packaging

The main purpose of the packaging currently used in the three delivery systems is to protect the products from air, light, and moisture. Packaging is product specific and the exact requirements must be defined before the most appropriate packaging technology for the product can be identified. The principal part of packaging is the barrier, generally provided by aluminum foil. As the thickness of the aluminum foil increases, the size of the microholes in the foil decreases creating a more effective barrier, but the cost per square meter increases. The packaging for sprinkles also typically includes a polyethylene layer for improved sealing and a paper or polyester layer for printing, and these layers are laminated for robustness. Studies for individual products need to consider local conditions to find the right packaging for the desired shelf life of the product in the countries of intended use.

For powder system products such as sprinkles, a foil with 9- $\mu\text{m}$  microholes and a 30- $\mu\text{m}$  polyethylene layer is commonly used. This type of packaging gives a shelf life of 18–24 months for powder-type products in Europe. Performance in developing countries is unknown. For products such as spreads, the packaging could include an aluminum foil with 12- $\mu\text{m}$  microholes whereas tablet blister packs typically use an aluminum foil with 20- $\mu\text{m}$  microholes. Opaque air-tight blister packs are preferred for tablets.

A low-speed packaging operation, ideally under nitrogen, is needed for spreads. A faster multilane operation can be used for sprinkles and tablets. Equipment that is fast and flexible will help to optimize the process and reduce the cost of packaging. Delivering an accurate product weight is critical to managing costs and decreasing the likelihood of overdosing. The ease with which packaging technologies can be transferred to developing countries must be considered when the packaging is de-

signed for a product intended for manufacture in the country of use.

Currently, all three CFSs are packaged as single servings. Products would be less expensive if the nutrients were in multiple-serving, child-resistant packages. In addition, single-serving packages present a waste disposal challenge. Tablets have an optimal storage life when packaged in individual opaque blisters because they contain hygroscopic compounds that are sensitive to humidity, especially in tropical climates. The sprinkles and spreads are difficult to package as multiple servings because they require the consumer to measure the servings. Although it is not critical to get an exact serving every day, day-to-day variations in serving size can be tolerated provided the average ingested over a few days is correct. More research is needed on the shelf life of multiple-serving containers of CFSs to ensure that an adequate shelf life is maintained in different environmental conditions and that the risk of overdosing is non-existent or negligible.

### Encapsulation Technologies

Encapsulation is a possible solution to micro- and macronutrient instability in a CFS, even under optimal packaging. In encapsulation the active ingredient is entrapped in a nonreactive matrix to physically protect it from destructive factors (e.g., oxygen, moisture, and light) or physically separate it from other reactive components (e.g., iron and vitamins). Encapsulation matrices can be prepared from either hydrophobic (lipid) or hydrophilic (carbohydrate or protein) components that entrap the active ingredient in single or multiple layers. The active ingredients are released when the encapsulating matrix is broken down, for example, by dissolution in water, elevated temperatures, physical destruction, and enzymatic degradation. The encapsulation technology must be product specific. Factors including the function of the encapsulated ingredient, processing and storage conditions that the encapsulated ingredient is exposed to, stability requirements of the entrapped encapsulated ingredient, and cost constraints must be considered to determine the appropriate encapsulation technology for a specific product. Because the thickness and the nature of the coating agent may decrease the bioavailability of the nutrient that is encapsulated, this needs to be considered as well. Although encapsulation systems can be maintained in CFSs, they may be destroyed when added to foods.

Encapsulation can physically separate iron from other nutrients, thereby decreasing its ability to promote oxidation and destroy vitamins or cause color changes in the food. Iron encapsulates made with gums and starch or maltodextrin have been shown to be effective in preventing iron-promoted lipid oxidation. Experience has shown that completely coating an iron molecule is important.

The presence of even small amounts of nonencapsulated iron can create problems associated with iron-promoted oxidation.

Sprinkles contain ferrous fumarate encapsulated in partially hydrogenated fat. The dispersible or crushable tablets do not use encapsulation technologies. Iron encapsulated in fats or carbohydrates is being explored for use in spreads. If fat-encapsulated iron is used in spreads, conditions must be controlled so that the encapsulation system does not disintegrate during processing and storage.

### Limiting or Eliminating Allergens in Spreads

Proteins incorporated in spreads can be allergenic. Peanut, milk, soy, and tree nut proteins used to prepare spreads are common food allergens. Data from the United Kingdom suggest that the incidence of near-life-threatening episodes due to food allergies is about 0.2 per 100,000 cases, with peanuts resulting in the most life-threatening cases (29). Although this is one of the very few papers on the prevalence of anaphylaxis, it may underestimate the real risk because the survey was conducted among pediatricians rather than all physicians. A study across the European Union (EU) reported that of the 535 serious anaphylactic reactions reported, 23% were caused by peanuts and 14% by tree nuts (30). Bock (31) estimates that about 950 severe allergic reactions to food occur in the United States annually, one-third of which are anaphylaxis caused by peanut.

Current U.S. and EU recommendations are to delay the introduction of highly allergic foods to children at high risk of developing atopy. When both parents or one parent and a sibling have allergies, a child is deemed at risk for atopy including food allergies (32,33). The above references suggest delaying the introduction of any foods that cause allergies in high-risk children until age 3 years. However, it has not been demonstrated that any food allergy can be avoided by this recommendation. Some studies suggest that milk allergy can be prevented by using hypoallergenic formulas, and there is epidemiologic evidence linking a higher prevalence of peanut allergy in children whose mothers ate more peanuts during pregnancy or who were given peanuts at an earlier age, but no controlled studies have been published demonstrating that delaying the introduction or restricting diets have an allergy-preventing effect (34).

The risk of food allergy should be weighed against the risks associated with undernutrition when protein-containing spreads are considered for use. The risk of allergy is likely much lower in a CFS target population than is the risk of undernutrition. Hundreds of thousands of metric tons of corn soy blends containing possibly allergenic soy are used every year in food aid programs worldwide without provoking a noticeable increase in food allergy or intolerance. Allergic reactions may be

subdued in undernourished children and also in those with parasitic and mycobacterial infections (35–37). The protein source of a spread can be changed where a food allergy is known to exist in the population. It is technologically possible to develop a protein-free spread that would still be valuable for improving the micronutrient quality of complementary food. The resulting spread, however, might be more susceptible to oxidation.

### Bacterial and Chemical Contamination

All CFSs should be prepared under hygienic conditions that comply with the *Codex Alimentarius* recommendation for infant food preparations (38). A theoretical risk exists for increasing pathogenic bacterial growth by adding a CFS to complementary food that is not eaten within 4 to 6 hours, because some micronutrients such as iron are needed for bacterial growth. The reality of this possibility needs to be investigated.

Chemical contaminants should be kept at minimal levels. For peanuts, special attention needs to be given to the level of aflatoxins. A maximum of 15 to 20 ppb of aflatoxin in peanuts should be allowed (39,40).

### Interactions Between Complementary Food Supplements and Complementary Foods

A CFS may be either taken separately or mixed with complementary foods. For sprinkles, and for spreads given to infants aged 6 to 12 months, only the latter option is possible. Ideally, CFSs are added after cooking because the encapsulation system is likely to be destroyed during cooking and a large proportion of the vitamin C may be oxidized if CFSs are boiled with food for more than a few minutes. Even if a CFS is added to complementary food after cooking, the vitamin C is likely to be oxidized within a few hours, more rapidly if the pH of the food is low (23).

Oxidative reactions in complementary foods are likely to increase with the addition of iron, especially if the iron is not encapsulated or if the encapsulation is destroyed after addition to the food. Off-flavors due to fat oxidation are unlikely to occur if the food is consumed within a few hours of preparation. However, vitamin oxidation may occur more rapidly than oxidation of lipids, leading to reduced micronutrient concentrations and reduced iron bioavailability when vitamin C is destroyed. For these reasons and also to avoid possible bacterial proliferation and fat oxidation, a CFS should be added after the complementary food is cooked and consumed soon after.

Iron and to a lesser extent zinc absorption are hindered by phytate in cereal gruel. Incorporation of a commercial phytase enzyme in a CFS is technically possible, but it is doubtful whether such enzymes could degrade sufficient phytate from the gruel to significantly improve bioavailability. Alternatively, specific acid-resistant phytases can

be added to degrade phytic acid during digestion in the stomach, but inclusion of active enzymes is not allowed by most standards and would lead to regulatory problems. An alternative approach is to degrade the phytase in the food itself before the CFS is added, through germination or fermentation.

### Flavoring Agents

Flavoring agents are compounds added in small amounts to mask unpleasant tastes or to increase the acceptability of a food by adapting it to the local taste. These compounds have different chemical forms (esters, ketones, alcohols, and aldehydes are among the most frequently used) but are usually highly reactive, volatile, hydrophilic, and sensitive to oxidation and light. Direct incorporation of flavoring agents into a CFS may reduce the shelf life, but this can be overcome with protective encapsulation and would increase the cost of the CFS.

Particular attention needs to be given to the sensory characteristics of the CFS, because infants and young children have taste preferences that differ from other age groups. This requires proper and appropriate sensory testing of the CFS after it has been added to different complementary foods in local environments to confirm that its sensory properties are acceptable for the population and age group of interest.

## OPERATIONALIZING COMPLEMENTARY FOOD SUPPLEMENT PRODUCTION

The long-term sustainable solution to improving the quality of complementary food is to make an acceptable CFS that is available in the commercial market at a price that most of households most in need can afford. A parallel distribution channel for a subsidized product, targeted to the most vulnerable, can be set up through the health or welfare system.

### Market Positioning of a Complementary Food Supplement

Positioning the product in a market requires that the target population and the product's comparative advantages are identified. For example, a spread can be positioned as a macro- and micronutrient CFS. Because it looks like a food, a spread can be sold through food outlets. Tablets and sprinkles can be positioned as dietary or health supplements through different channels, including pharmacies and general stores selling basic medicines such as aspirin and antimalarial drugs. Clearly the input of marketing experts knowledgeable about local perceptions, beliefs, taste preferences, and purchasing practices is needed.

### Cost Positioning of Different Complementary Food Supplements

The estimated cost of production for a single daily dose of the current formulations (the amounts of nutrients delivered determined by the formulation of the product) is U.S.\$ 0.01–0.03 for dispersible tablets and U.S.\$ 0.025–0.03 for sprinkles. These prices will vary according to the number and concentration of the micronutrients in the products and the type of manufacturing technology required. Eventually, the cost difference of these two products will be related to the relative cost of compressing a product and putting it in to a blister pack versus the packaging of an equivalent dose in an individual sachet.

Spread costs are estimated to be U.S.\$ 3/kg. If 20 g of the spread provides the daily micronutrient dose, the cost becomes U.S.\$ 0.06 per day. Because the cost of the spread base is higher than the micronutrients it contains, increasing the concentration of micronutrients in the spread will reduce the price per dose.

The production cost of tablets or sprinkles is always likely to be lower than the cost of producing the spread even if the spread is prepared with a high concentration of micronutrients. Spreads could be packaged in multiple-serving containers, but this would have only a marginal effect because the major cost is putting the spread in the container.

The cost of a CFS needs to be compared with the cost of other options available in the market. A nutrient-by-nutrient comparison is needed in which the cost of one RNI from the CFS is compared with the same amount of nutrient obtained from locally available, highly nutrient-dense foods (for spreads) or pharmaceutical preparations (for tablets and sprinkles). For iron and zinc, these comparisons should be corrected for relative bioavailability. A rigorous analysis would calculate the minimum cost needed to design a balanced ration with and without the use of the CFS, for example, through linear programming (41). The CFS could then be promoted on the basis that it reduces the price of a balanced ration.

### Regulatory Requirements

Relevant national and international guidelines and regulatory requirements for foods intended for infants and children must be followed in developing a CFS. The amounts of nutrients added to a complementary food must be consistent with the relevant national recommendations for daily dietary intakes or, in their absence, the FAO/WHO RNI (15). The forms of nutrients added and the overall formulation of the product should be consistent with the *Codex Alimentarius* recommendations for foods for infants and children (42).

Whether the CFS is considered a food or a dietary supplement under the national regulations will determine

the regulatory requirements that must be met by the product before and during its marketing in the country. Spreads, in their current form, clearly fit within the *Codex Alimentarius* definition for formulated supplementary foods for older infants and children (43), but the situation for the dispersible micronutrient tablets and sprinkles needs to be determined at the local level.

### Complementary Food Supplements Production and Technology Transfer

Industrial production of the three CFSs can be implemented rapidly in many developing countries where factories have the appropriate equipment. Production could start with minimal capital investment.

The dispersible tablets are made by direct compression of bulk micronutrient premixes. This is a simple procedure for any pharmaceutical company with a tablet-producing facility. The production of zinc and iron dispersible tablets will start soon in Bangladesh.

Sprinkles require an adapted packaging installation that is available in many food and pharmaceutical factories worldwide. To date they have only been produced on a small scale in Canada. Where the equipment to produce sachets is not available, sprinkles sachets could be imported, but this will make the product more expensive.

Industrial production of the therapeutic fortified spread that is used in relief operations is already underway in France. Spread production relies on a simple technology that can be implemented in any industrial bakery, which in many developing countries does not operate at full capacity during the day because most bread is made at night. Packaging should be adapted to the local conditions. Production of a preventive spread could in principle build on existing local programs that make the therapeutic spread to treat severe undernutrition. A pilot scheme to produce therapeutic spread is ongoing in Malawi, and others are scheduled to start in Niger and Senegal. The experience gained from these pilot programs will provide relevant information for local production of the preventive formulation and also on shelf life and distribution issues.

### Quality Assurance and Control

Quality assurance identifies and monitors the key quality characteristics of a product and the critical control points in production and establishes corrective actions that must be taken at each step. Critical control points for all three CFSs have been identified in the pilot plants located in developed countries. Accurate dosing of the premix and testing the finished product for nutrient levels at production, storage, and different distribution points, for example, are critical quality criteria for any CFS. The nutrients used as indicators, however, are product specific and need to be determined on the basis of the

**TABLE 4.** Knowledge gaps limiting CFS utilization

Dispersible tablet and sprinkles	Spreads	All CFS
Determine the technical feasibility of including multiple micronutrients	Determine the optimal balance between macro- and micronutrients	Evaluate the effect of different encapsulation techniques on absorption of minerals, especially iron
Determine the technical feasibility of adding multiple micronutrient CFS to different complementary foods	Develop encapsulation techniques, especially for iron, adapted to spreads	Evaluate the use and acceptability of NaFeEDTA as the source of iron
Determine whether to position as a food or dietary supplement	Establish the optimal antioxidant and functional properties of proteins included in the spread	Evaluate the effect on bacterial growth and fat oxidation of adding CFSs to complementary foods
	Establish the optimal combination of different antioxidants and their effect on mineral absorption	Determine the feasibility of multiple-serving packaging
	Evaluate the effect of local protein sources on lipid oxidation, iron bioavailability, and texture	Determine the shelf life under different ambient conditions
	Identify the criteria for selecting ingredients in the country of production	Identify the most appropriate packaging for the desired shelf life of the product
	Determine the maximum shelf life of spreads prepared with locally available ingredients with standard packaging	Evaluate the sensory characteristics and acceptability of adding CFSs to complementary foods in different environments
	Determine the minimum shelf life needed for distribution through commercial channels	Determine the efficacy of CFSs in a preventing micronutrient malnutrition
		Evaluate the effectiveness of CFSs in a preventing micronutrient malnutrition
		Determine the cost positioning of CFSs
		Evaluate the transferability of technology from developed to developing countries
		Develop an in-country communication strategy to promote CFS use

nutrients added to the product. Provided that the quality of the premix is ensured either through certification from the premix supplier or testing by the manufacturer before addition to the product, testing the CFS for the level of a single appropriate nutrient can be an adequate indicator of the levels of the other nutrients added to the product. Checking for oxidative rancidity is a key quality control measure for spreads susceptible to oxidation because of their high fat content.

### Public-Private Sector Partnership and Coordination

The three CFSs have been developed by private companies or individuals at their own risk, although the sprinkles have received external donor funding. The spreads are protected by a (French) patent and a (Canadian) patent application has been submitted for the sprinkles. The formulation for the tablets is not protected by patent and can be made by any pharmaceutical company.

The development, evaluation, and promotion of CFSs are at the interface of private and public interests and it is important that public funds are not used to create an unfair monopoly situation. The level of a fair retribution for private sector research and development efforts—compatible with large-scale use in public health programs—should be clarified at an early stage in the public-private sector dialogue.

### Summary and Knowledge Gaps

Complementary food supplements are a new and promising approach for reducing multiple micronutrient

deficiencies in infants and young children living in developing countries, but important knowledge gaps exist (Table 4). Intervention trials are needed to determine the efficacy of CFSs in preventing micronutrient deficiencies; other important gaps relate to technical and operational issues. For example, even though sprinkles and tablets are produced using well-known technologies, further research is needed to successfully modify them for use as a CFS. The development of the spread is not as advanced as the other two products and further research is needed to improve the technology. Although the products are not ready for widespread use, enough information is available to set the research priorities and accelerate the development and implementation of products deemed most likely to improve the micronutrient status of millions of children around the world.

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