New Approaches for Designing and Evaluating Food Fortification Programs

Lindsay H. Allen

U.S. Department of Agriculture, ARS Western Human Nutrition Research Center, University of California, Davis, CA 95616

ABSTRACT Historically, food fortification programs were often undertaken with little attention to issues such as micronutrient bioavailability, optimal levels of addition, or efficacy or to monitoring impact on nutritional status, health, and human function. Several developments in recent years have enabled substantial progress to be made in the design and evaluation of fortification programs. The methodology for estimating the prevalence of inadequate nutrient intakes in a population and tolerable upper intake levels has been established and can be used as the basis for estimating desirable amounts of nutrient addition. More attention is being paid to assessing the bioavailability of nutrients (especially minerals) using stable and radioactive isotopes, and bioavailability of iron compounds can be estimated from changes in total body iron calculated from the ratio of transferrin receptors to serum ferritin. Procedures for quality control of the fortification process have been established. New approaches to monitoring the impact of fortification over time include assessment of liver retinol stores using retinol isotope dilution. In summary, the design and evaluation of food fortification programs now requires a series of formative research procedures on the part of nutritionists, which were not often expected or conducted in the past. J. Nutr. 136: 1055–1058, 2006.

KEY WORDS: • fortification • design • micronutrient • evaluation

Food fortification programs have been designed to restore nutrients removed during food processing (e.g., restoration of thiamin, riboflavin, niacin, and iron to white flour), to replace nutrients in substitute foods (e.g., the addition of vitamins A and D to margarine, a replacement for butter), or to correct obvious deficiencies in populations (e.g., iodine fortification of salt). However, inadequate attention has been paid to the quantities of nutrients added as fortificants, their bioavailability, or the effect of fortification on the nutritional status of the recipient population. These questions become increasingly important now that many more countries, including those in the developing world, turn to fortification to supply a substantial part of their micronutrient requirements. In developing countries, fortification has become a more realistic option because of the increasing intake of centrally processed foods. Although many households still do not consume processed cereals, fortification of condiments, sugar, sprinkles that can be added to foods just before serving, or spreads may be alternative options (1).

Several recent developments have led to the recognition that a great deal more attention needs to be paid to the design and evaluation of food fortification programs. These include the establishment of estimated adequate intakes for the United States and Canada, with accompanying methods for designing and evaluating nutrient intakes for population groups (2,3). The Dietary Recommended Intakes for these countries now provide tolerable upper intake levels (ULs)3 for nutrients, as do several other agencies such as the World Health Organization (WHO)/Food and Agriculture Organization (FAO) (4). Recently, the World Health Organization has published new “Guidelines for Micronutrient Fortification of Foods,” which includes information on how to plan, monitor, and evaluate micronutrient fortification programs (5). More details of much of the information covered in this article can be found in these Guidelines.

Designing fortification programs. A substantial amount of information is needed before a fortification program can be designed appropriately (Table 1). Initially there is some existing information on the prevalence of clinical symptoms of deficiency in the target population(s), or blood or urinary values indicating deficiencies of specific nutrients. However, such data are inadequate to design programs because they are usually collected from nonrepresentative samples of the population groups to be targeted, the nutritional status of many micronutrients is often not known, and infections can increase or lower blood or plasma levels of several important nutrients. Perhaps most importantly, biochemical data do not inform us about how much of each nutrient should be added as a fortificant. Thus,

---

1 Presented as part of the symposium “Food Fortification in Developing Countries” given at the 2005 Experimental Biology meeting, April 5, 2005, in San Diego, CA. The symposium was sponsored by the American Society for Nutrition and the Society for International Nutrition Research and was supported in part by an educational grant from Akzo Nobel, Inc. The proceedings are published as a supplement to The Journal of Nutrition. The supplement is the responsibility of the editors to whom the Editor of The Journal of Nutrition has delegated supervision of both technical conformity to the published regulations of The Journal of Nutrition and general oversight of the scientific merit of each article. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors or the publisher, editor, or editorial board of The Journal of Nutrition. Guest editors for the symposium are Jere D. Haas and Dennis D. Miller, Cornell University, Ithaca, NY. Guest Editor Disclosure: Jere Haas and Dennis Miller have no relationships to disclose.

2 To whom correspondence should be addressed. E-mail: lhallen@ucdavis.edu.

3 Abbreviations used: EAR, estimated average requirement; EDTA, ethylenediaminetetraacetic acid; FAO, Food and Agriculture Organization; RNI, recommended nutrient intake; UL, upper tolerable intake level; WHO, World Health Organization.
Clinical and biochemical data can suggest which micronutrients definitely need to be added to the food supply but will miss other micronutrient deficiencies, and cannot inform us about which foods to fortify or how much of each fortificant nutrient to add.

Existing information on usual dietary patterns can also point to the probable risk of specific nutrient deficiencies. For example, where animal-source food intake is low, there will be a higher risk of inadequate intakes of vitamin B-12, riboflavin, vitamin A, and bioavailable iron and zinc (6). High phytate intakes are an indication that intakes of absorbable iron and zinc might be inadequate. Low consumption of fruits and vegetables is a risk factor for inadequate intake of folate and vitamin C. However, as with biochemical data, information on dietary patterns is inadequate for providing us with acceptable information on which nutrients to add, which foods to use as vehicles for fortification, and how much of each nutrient should be added.

The most important information to obtain for the purpose of designing food fortification programs is the usual food intake of population subgroups. Information on usual food intakes can enable us to determine the prevalence of inadequate intakes of specific micronutrients by population subgroups, which food vehicles are good candidates for fortification, and what impact fortification with specific micronutrients will have on the prevalence of inadequate and excessive intakes of these nutrients.

**Calculating the amount of micronutrients to add.** In the past, levels of addition of micronutrients as fortificants were often based on levels used elsewhere, with little evidence of efficacy or effectiveness, although some consideration was usually given to the cost of each fortificant and whether there would be any adverse sensory effects. Another common strategy has been to plan the fortification level to supply the Recommended Dietary Allowance (RDA) for specific micronutrients by population subgroups, which food vehicles are good candidates for fortification, and what impact fortification with specific micronutrients will have on the prevalence of inadequate and excessive intakes of these nutrients.

**Measuring the bioavailability of nutrients added as fortificants.** In the past, little attention was paid to measuring the bioavailability of nutrients added to foods. For example, until recently it was not certain that the forms of iron added to wheat flour in the United States were absorbable (8–10). It is becoming increasingly recognized, however, that information is needed on the absorption of nutrients from different forms of fortificants, when added to a range of foods, and at different levels of addition. Another concern is potential adverse interactions among added micronutrients. Most research on these questions has been conducted on minerals, given their limited bioavailability in some situations.

**TABLE 1**

<table>
<thead>
<tr>
<th>Information needed for designing a food fortification program</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intake and nutritional status of population groups</strong></td>
</tr>
<tr>
<td><strong>Appropriate food vehicles and fortificants</strong></td>
</tr>
<tr>
<td><strong>Bioavailability of nutrients from food vehicles</strong></td>
</tr>
<tr>
<td><strong>Effect of fortificants on stability and sensory qualities of food</strong></td>
</tr>
<tr>
<td><strong>Simulation of the impact of fortification levels on nutrient intake adequacy and safety</strong></td>
</tr>
<tr>
<td><strong>Efficacy trials</strong></td>
</tr>
<tr>
<td><strong>Effectiveness trials</strong></td>
</tr>
</tbody>
</table>

The steps by which recommended levels of fortification are estimated from intake data are described in detail in the WHO guidelines but can be summarized as follows. First, the usual distribution of nutrient intakes is measured in specific population subgroups, including those suspected of being at the highest risk of deficiencies. This requires collection of 2 days of quantitative intake data on about 200 people per subgroup. The groups at greatest risk of inadequate nutrient intakes can then be confirmed from the intake data. The food intake data will also provide information on the distribution of intake of potential food vehicles (e.g., grams of wheat flour per day). This information is required for calculating the total amount of a nutrient that will be consumed by different population subgroups after fortification of each potential vehicle. The final step is to simulate the effect on the prevalence of inadequate intakes (percentage below the EAR) and excessive intakes (percentage above the UL) of adding different levels of each micronutrient to specific food vehicles.

In practice, the level of addition of fortificant micronutrients to individual foods often is constrained by several factors. One is technology, such as whether there may be undesirable flavor, color, or texture changes in the food. Another is safety, as it is important for virtually all consumers of the fortified food to consume less than the UL. For such reasons, it may be necessary to add the fortificant nutrient(s) to several foods or to fortify specific foods targeted to special population groups (to meet the high nutrient requirements of pregnant women or the high nutrient density requirements of foods for young children, for example). Another scenario, which was implemented in Costa Rica, is to fortify different foods with different micronutrients (e.g., sugar with vitamin A, flour with B vitamins and iron, and salt with iodine). The cost of the fortified food must remain low enough not to affect production or purchasing and to ensure program sustainability.

The most common strategy for measuring absorption of nutrients from fortificants has been to label the specific nutrient with radioactive or stable isotopes. This approach has been used to compare the absorption of $^{55}$Fe-labeled ferrous sulfate and $^{59}$Fe-labeled ferrous bisglycinate from whole maize (11) and the absorption of labeled iron from ferrous sulfate, ferrous bisglycinate, and Fe-EDTA from wheat and maize (12). Few investigators have measured changes in the efficiency of absorption of nutrients at different levels of intake, although one such example is measurement of the fractional and total absorption of $^{57}$Co labeled zinc consumed by children in 2 meals a day (13). The efficiency of absorption of the zinc...
fortificant fell with increasing level of addition, which is important knowledge for planning a zinc fortification program. The effects of adding EDTA on the absorption of several minerals can also be assessed; for example, a study in Sri Lanka showing that adding Na₂EDTA to rice flour increased the absorption of labeled iron and zinc fortificants (14). Another approach to answer the question of whether zinc fortificants impair iron absorption is to assess the effect on anemia recovery of adding different levels of zinc to iron-fortified flour (13).

Assessing the efficacy of fortificants. With the techniques described above, more attention is being paid to assessing the efficacy of micronutrient fortification strategies for improving nutritional status and human function and health, although examples are still limited. An obvious approach is to assess the effect of fortified foods on hematological and biochemical measures of nutritional status. In the case of zinc, daily consumption of zinc-fortified bread was shown to increase the serum zinc concentrations of Turkish school children (15). Salt fortified with both iron and iodine improved hemoglobin, ferritin, and transferrin receptor concentrations more than iodine fortification alone (16). Provision of a drink fortified with multiple micronutrients improved iron, folate, and riboflavin status of schoolchildren in Botswana (17); however, neither vitamin A nor vitamin B₁₂ status improved significantly, probably because insufficient amounts of these nutrients were added.

In the case of iron fortification, one important new development has been the use of the serum transferrin receptor to ferritin ratio to measure change in total body iron stores resulting from fortification, based on a formula developed by Cook et al. (18). The change in body iron stores is a quantitative, sensitive (especially compared with change in hemoglobin concentrations), and specific measure of the amount of iron absorbed during the period when a fortified food is consumed. This approach has been used by Zimmerman et al. (19) to demonstrate that micronized ferric pyrophosphate is well absorbed when added to iodine- and vitamin A–fortified salt in Morocco (19); compared with iodized salt alone, body iron was more than twice as high after 5 months and almost 5 times as high after 10 months.

Efficacy trials that show the anticipated beneficial effect of a fortificant on nutritional status are often used to advocate fortification programs. However, there are far fewer examples where the effectiveness of programs has been evaluated. One example is the recent efforts to evaluate the effectiveness of folic acid fortification (20), although, as is usually the case when a population's food supply is fortified, there was no placebo group.

Effects of fortification on human health and function. Ideally, in addition to demonstrating improvements in nutritional status, it is desirable to show that fortification programs improve the health and function of the populations to which they are provided. Historical examples of such improvement include the substantial reduction in B vitamin deficiencies in the United States (21), of vitamin D rickets and deficiency through fortification of dairy products (22), and of iodine deficiency through salt fortification in countries such as Switzerland (23) and the United States (24). More recently, folic acid fortification of flour has paralleled reductions in the incidence of neural tube defects in the United States and Canada (20). Few such programs have had a nonintervention control group, making it difficult to be certain that other dietary or nondietary changes did not explain the observed trends in nutritional status, although accompanying improvements in status of the specific nutrient would tend to rule out the latter explanation. In the United States and Canada, a reemergence of vitamin D deficiency and rickets has been attributed to low consumption of vitamin D–fortified dairy products (25). Zimmerman et al. (16) demonstrated that the addition of iron to iodized salt (compared with iodized salt alone) significantly improved the effects of the fortificant iodine on thyroid function and reduced thyroid size in iodine-deficient anemic children in Morocco (16). Much more work is needed to define the effects of fortification on public health, in addition to nutritional status.

Monitoring. There are several important aspects of monitoring fortification programs. One is quality control, which includes industry monitoring, legal monitoring, household monitoring (presence of fortified food in households), and evaluation of the adequacy of coverage and amounts of fortified food consumed. These technical aspects of monitoring have been described in detail elsewhere (5). Indicators of the performance of programs include provision (number of products fortified, stores selling fortified products, and the percentage of the population with access to the fortified foods); utilization (percentage of households or individuals who purchase fortified food, the amounts and frequency of purchase, and the percentage of households who have food fortified at the minimum level); and coverage (percentage of individuals consuming the fortified food and amounts and frequency of intake).

Impact evaluation includes the change in intake of the micronutrients targeted for fortification and changes in the prevalence of specific micronutrient deficiencies and related health problems over time. A relatively recent example of impact evaluation is seen in the effects of folic acid fortification of flour in countries such as the United States, Canada, Australia, and Chile. Although there were no nonintervention control groups, trends for an increase in folate intakes (26,27) and improvement in status (26,27), and a reduction in the incidence of neural tube and other birth defects (20,27,28) and plasma homocysteine concentrations (26) have been assessed in relatively large population samples. Folic acid intakes in the United States increased by more than twice the level predicted (29), as there has been a trend for voluntary fortification of other foods by manufacturers. It is always important to monitor this possibility.

Similarly, it is critical to monitor the risk of excessive intakes of the added nutrients. The prevalence of intakes above the UL can be monitored by collection of food intake data, although ULs do not exist for some nutrients. Excessive body iron accumulation can be monitored from measures of serum ferritin and transferrin receptors using the model of Cook et al. (18), as discussed above. Excessive accumulation of liver vitamin A has been measured using retinol isotope dilution. This method was more sensitive than changes in serum retinol concentrations for detecting changes in vitamin A status as a result of retinol fortification of sugar in Nicaragua (30). The amount of unmetabolized folic acid in the circulation has been proposed as an indicator of excessive folic acid intake from fortified foods (31). Other adverse outcomes that must be monitored might include mortality from various chronic diseases (32) and improved pregnancy outcomes.

Summary. The developments discussed in this article, and the current trend toward increased food fortification at the global level, mean that nutrition scientists should be heavily involved in the design, evaluation, and monitoring of food fortification programs.

LITERATURE CITED