Science-based micronutrient fortification: which nutrients, how much, and how to know?\textsuperscript{1,2}

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This issue of the Journal includes a comprehensive biochemical assessment of folate status in a representative sample of the American population in the National Health and Nutrition Examination Survey (NHANES) 1999–2000 (1). This survey represents the largest, but not the first, documentation of folate status since the mandatory folic acid fortification of flour and grain products was initiated in the United States in 1998. As was shown in other populations (2–5), folate status in the NHANES 1999–2000 population has improved remarkably since the initiation of folic acid fortification. Mandatory folic acid fortification may be the most important science-driven intervention in nutrition and public health in decades. The study by Pfeiffer et al (1) reminds us that there is still work to be done and a need for protocols that assign responsibility and resources for the evaluation of public health interventions that affect large sections of the total population of the United States and other countries.

A sign in a health food store caught my eye in the 1980s, shortly after I'd agreed to serve on a Federal Drug Administration (FDA) panel to assess communication concerning the over-the-counter marketing of vitamins in the United States. The sign read, “God gave us vitamins and the FDA is taking them away.” Then, as now, we were faced with a passionate certainty about the value of particular interventions and remedies or about the harm of others and with the substitution of transcendent beliefs for scientific analysis. In sharp contrast, the case study of folic acid fortification as an approach to prevent neural tube defects is a latter-day example of the application of meticulously controlled scientific trials to insightful previous hypotheses and observational studies. These controlled trials led the FDA to mandate folic acid fortification of the diet. Although folic acid is not the natural food form of this vitamin (6), folic acid fortification has served wonderfully in preventing and treating periconceptional period for the prevention of spina bifida and other related neural tube defects (7).

The importance of folic acid supplementation during the periconceptional period for the prevention of spina bifida and related neural tube defects has been extensively reviewed (8). The meticulous process by which the FDA arrived at the mandated level of fortification consisted of an extensive analysis of food intake, the consideration of other supplemental vitamin intakes, and a review of the best safety data available concerning the ≈280 million people who would be exposed. Having been one of those who strongly supported food fortification as the most feasible approach to increasing folic acid intakes in women before conception, I will not now criticize a process that was imperfect in the sense that it lacked an empirical and science-based plan for monitoring and evaluating the effectiveness and safety of this large-scale intervention. Despite a great deal of effective, although at times discordant, interaction between the 3 sections of the Department of Health and Human Services (FDA, Centers for Disease Control and Prevention, and National Institutes of Health), there was, at the time the decision was made to mandate the addition of folic acid to enriched flour, no coherent plan to monitor the national and regional effect on neural tube defect births, to document actual changes in folate status, or to assess the possible occurrence of untoward effects on the population. Although evaluations of the effect of folic acid fortification on folate status, homocysteine concentrations, and neural tube births were conducted, the relative responsibilities of the 3 federal agencies for the evaluation of this major public health intervention have not been clear. In particular, none of these agencies was assigned the responsibility of monitoring the safety of this intervention. Yet, despite initial positive effects of the folic acid fortification of flour and grain on folate status and on the prevention of neural tube defects, the possibility remains that certain segments of the exposed population may benefit less and may even experience some adverse effects from an increase in folic acid intakes, which have turned out to be even greater than originally modeled in premadicate predictions.

The synthesis of folic acid by Lederle Labs in 1947 was one of the milestones achieved during the era of discovery of vitamins in the first half of the 20th century. This stable and unreduced form of folate has served wonderfully in preventing and treating folate deficiency and for much of the study of folate biology. However, folic acid is not the natural form of the vitamin as it exists in food, and evidence suggests that concentrations of unmetabolized folic acid in the blood after the ingestion of supplements or fortified foods may have different effects on folate binding proteins and transporters (9). The tolerable upper level of folic acid intake, set forth recently by the Institute of Medicine in the Dietary Reference Intakes (10), warrants continuing consideration, especially the publication’s emphasis on the possible

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adverse effects of high folic acid intakes in persons with a poor vitamin B-12 status. Questions raised by these tolerable upper levels emphasize the importance of establishing protocols for evaluating the safety and effectiveness of folic acid fortification interventions with the use of the best scientific information available.

The World Health Organization recently held a consultation in an effort to lay out the kind of decision-making process that many countries will undergo as they consider the fortification of food products with micronutrients. Policy decision making in any country considering fortification with one or several micronutrients should not be limited to the documentation of the indications for fortification, the food or foods used to deliver the nutrients, the expected bioavailability of the nutrient, or even the dose of the fortificant. A plan for evaluating the effectiveness and safety of the intervention is also needed. Although such an evaluation may be costly, the target population of a nationwide or global intervention deserves to be informed about its effectiveness with regard to health promotion, disease prevention, and safety. Nutrition scientists have a major role to play in designing these evaluative protocols. The agencies responsible for national or international implementation of food fortification programs must be ready to accept the responsibility and to provide the funds for these evaluations.

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REFERENCES