

## Special Article

# The History and Future of Food Fortification in the United States: A Public Health Perspective

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*For more than 50 years, the United States federal government has regulated food fortification. During this time, the nutritional situation in the United States has improved greatly, whereas scientific information about the role of vitamins and minerals in human growth and development has increased exponentially. Concurrently, government authority to regulate food fortification has declined. This paper provides a brief history of U.S. food fortification policy and describes the contribution of food fortification to U.S. nutrient intakes. The paper highlights future directions of food fortification in the United States in light of these important developments, and addresses the issue of risk and the need to balance deficiency and toxicity in a generally well nourished population.*

**Key Words:** food fortification, government regulation, U.S. Policy, nutrient intakes, risk and balance of deficiency and toxicity

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### Introduction

Scientific understanding of the role of vitamins and minerals in human growth and function has increased greatly in recent decades. Researchers working in laboratory and clinical settings have deepened scientific understanding of the functional effects of micronutrient deficiencies.<sup>1</sup> Other advances have come through nutritional epidemiology. For example, clinical trials have established a relationship between low folate intake and increased risk of neural tube defects, whereas prospective cohort studies have identified an association between elevated homocysteine and cardiovascular disease.<sup>2,3</sup> In developing countries, research has greatly increased information about the consequences of micronutrient deficiencies such as iron deficiency, which influences the

cognitive and school performance of millions of children.<sup>4,5</sup> Vitamin A and zinc deficiency are now recognized as major contributors to child mortality and morbidity in the developing world.<sup>6-9</sup> Depending on their applicability, U.S. public health programs and policies should respond to these new developments.

The fortification of food with added vitamins and minerals has long been an important approach to preventing micronutrient deficiencies. This paper considers future directions of food fortification in the United States in light of scientific advances in micronutrient nutrition. To provide a foundation, the article reviews the history of U.S. food fortification policy, and then describes the contribution of food fortification to U.S. nutrient intakes. Finally, the paper addresses the issue of risk, and the need to balance deficiency and toxicity in a generally well nourished population.

### A Brief History of Food Fortification in the United States

#### *The Prewar Years (1924-1940)*

Food fortification in the United States began in 1924, when iodized salt was first introduced in Michigan.<sup>10</sup> Subsequently, the prevalence of goiter fell from 38.6% to 9%. To obtain marketing advantage, industry soon introduced iodized salt throughout the United States.<sup>11</sup> By the 1930s, iodine deficiency had been virtually eliminated as a serious public health problem.

The iodization of salt was nearly coincident with a revolution in the nutritional sciences. In 1912, Funk<sup>12</sup> hypothesized that beriberi, pellagra, and scurvy were due to inadequate intakes of "vitamines." At approximately the same time, McCollum and Davis<sup>13</sup> identified a fat-soluble factor (vitamin A) that was necessary for the growth of rats. By 1930, Karrer had elucidated the structure of vitamin A, and scientists during the next decade quickly identified the structures of three additional fat-soluble and seven water-soluble vitamins.<sup>14,15</sup> With the synthesis of several vitamins on an industrial scale, the door was opened to the fortification of the U.S. food supply with synthetic essential nutrients. As with iodine, the newly identified vitamin deficiencies could be

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eliminated by scientifically altering the nutritional content of the U.S. food supply.

The public health need for food fortification was evident in the late 1930s. Vitamin and mineral deficiencies were prevalent in the U.S. population. In the southeast, pellagra (niacin deficiency) had emerged as a major killer owing to a diet based on over-milled corn meal, molasses, and fatback bacon. An estimated 25,000 cases of pellagra were identified during the years 1907 to 1912, and approximately 40% of these cases were fatal.<sup>16</sup> At the peak of the epidemic (1928–1930), nearly 7000 individuals per year died from pellagra, and perhaps 200,000 persons suffered from less severe niacin deficiency.<sup>17</sup>

In the northeastern United States, rickets was a common disorder of children with an estimated 75% of infants in New York City afflicted in 1921,<sup>18</sup> and a reported 339 rickets deaths around the country in 1933.<sup>19</sup> Infant scurvy was common in many urban areas,<sup>20</sup> and cases of beriberi (thiamin), ariboflavinosis, and night-blindness (vitamin A) were encountered occasionally by both physicians and public health workers.<sup>21</sup> In 1935 to 1936, Stibling and Phipard surveyed 4000 families and estimated that approximately one-third of American families had “bad” diets.<sup>22</sup> Examinations of 400 consecutive patients admitted to the Stanford University Hospital in 1940 to 1941 revealed 11% of patients with “definite signs of vitamin deficiency.”<sup>23</sup>

### **Establishment of the First Recommended Dietary Allowances and Federally Regulated Food Fortification**

In response to high rates of malnutrition and fears of potential U.S. involvement in war, President Roosevelt called a National Nutrition Conference for Defense, which met in May of 1941.<sup>24</sup> At this meeting, the Committee on Food and Nutrition of the National Research Council (now the Food and Nutrition Board) presented the first Recommended Dietary Allowances (RDAs).<sup>25</sup> The new RDAs covered energy, protein, two minerals (iron and calcium), and six vitamins (thiamin, riboflavin, niacin, ascorbic acid, and vitamins A and D). These new allowances were, “based on objective measurements of minimum requirement, to the average of which in the case of each nutrient is added what is scientifically deemed to be a reasonable allowance to cover individual variations plus a modest margin of some individual nutrients, in recognition of the difference between minimal-adequate and optimal intakes.”<sup>26</sup>

Depending on the nutrient, the RDA was based on balance studies, depletion-repletion studies, and some educated guessing. From the start, “one of the first assigned functions was to formulate quantitative goals to serve as a basis of reference in planning diets and food supplies.”<sup>26</sup>

Also arising from the National Nutrition Conference were a series of recommendations, including, “improving the nutritive value of certain low-cost staple food products, such as flour and bread, by enrichment with nutritive elements that have been removed from them by modern milling and refining processes. Pending further developments in the milling of grains so as to retain their full, natural, nutritive values, enrichment is an economical way to improve American dietaries almost universally, without interfering with deeply ingrained food habits. *The method, however, should be used with discretion and only on the basis of findings of medical and nutritional experts* [italics added].”<sup>26</sup>

The Committee on Food and Nutrition favored “appropriate enrichment of flour and bread (and perhaps corn meal), the fortification of milk with vitamin D, the suitable addition of vitamin A to table fats [margarine] and of iodine to salt for dietary use.”<sup>27</sup> The new RDAs would serve as the “yardstick” for fortification. Thus, the RDAs and federally regulated food fortification were linked, both having their origins in new scientific knowledge, growing public health and national security concerns about the high prevalence of malnutrition, and the technical ability to add synthetic vitamins to food at relatively low cost.

The Committee on Food and Nutrition expressed concerns about the fortification of food in the absence of regulatory oversight, and stressed that it was “opposed to *indiscriminate* fortification of general purpose foods with vitamins or minerals or dietary essentials.”<sup>27</sup> Instead, the Committee enunciated basic principles to guide appropriate food fortification. First, fortification was only indicated when “there exist deficiencies of vitamins and minerals in the diets of significant segments of the population. . . which cannot promptly be corrected by public education. . .” If such conditions were met, then:

- the Committee endorsed the addition of specific nutrients to staple foods to prevent deficiencies in “the general population, or of significant. . . geographic, economic, or racial segments.”<sup>27</sup>
- fortification should be restricted when possible to “those foods which have suffered losses in refining processes and. . . the vitamins and minerals added to such foods should preferably be the kinds and quantities native therein in the unrefined state.”<sup>27</sup> [Restoration of nutrient losses via additions of vitamins and minerals has sometimes been termed *enrichment*, and has been contrasted with *fortification*, which in a narrow sense may be defined as the addition of nutrients in excess of natural quantities. For the purposes of this review, fortification is used more broadly as the addition of nutrients to foods.]
- the addition of nutrients above “natural levels. . . may be sanctioned when more natural routes are practi-

cally unavailable as ways to correct known nutritional deficiencies."<sup>27</sup>

- "the Committee opposes the addition of synthetic vitamins to carbonated beverages and confectionary."<sup>27</sup>

Under authority obtained through the *Federal Food, Drug and Cosmetic Act* (1938), the Food and Drug Administration (FDA) would encourage and regulate food fortification by *standards of identity* (such as "enriched flour") that specified what nutrients were to be added to food and in what quantities. If industry deviated from these specifications and labeled the food as "enriched," then the Food and Drug Administration could prosecute on the basis of the food being "misbranded." Nonstandard food formulations would be discouraged by strict labeling requirements.

On January 1, 1942, the FDA formally established a standard of identity for enriched white flour (fortified with iron, thiamin, and niacin). Additions of riboflavin and calcium were optional. With production of sufficient synthetic riboflavin to meet the needs of industry, riboflavin was added to the standard of identity in 1943. The quantity of vitamins and iron added to bread and flour are reported to have been calculated as the amount of nutrient needed to meet the RDA if the consumer ate the nation's average of six slices of bread per day.<sup>10</sup>

With the end of the Second World War, the FDA quickly established formal standards of identity for enriched pasta (1946), white bread (1952), corn meal and grits (1955), and white rice (1958). These new enriched foods were variants of the white flour formulation, containing additions of iron, riboflavin, niacin, and thiamin. By 1954, a major nutrition textbook would report "frank deficiency diseases have been virtually eliminated from this country, due largely to the work of medical, public health and nutrition authorities."<sup>28</sup>

### **Attenuation of FDA Power to Regulate**

In 1962, the FDA noted that there had "been many advances in the science of nutrition and its commercial applications to products that are represented or which purport to be foods for special dietary uses."<sup>29</sup> Manufacturers during the 1950s had increasingly marketed dietary supplements and fortified foods, often using unsupported health claims. The FDA now proposed to regulate these products based on current scientific information. This action engendered stiff opposition from both industry and the public.<sup>30</sup> In 1966, after 4 years of testimony, the FDA finally published its new regulations: standards of identity were established for both dietary supplements and fortified foods.<sup>31</sup> Henceforth, the FDA proposed to tightly regulate dietary supplements and fortified foods by specifying which nutrients were permitted and in what amounts. Moreover, the FDA would greatly restrict product labels and marketing claims.

Just days before the new regulations took effect the FDA, under heavy fire, delayed implementation.<sup>30</sup> In 1974, after years of hearings and testimony, the FDA proposed a much relaxed set of fortification and labeling regulations. Among the new regulations were an expanded set of principles to govern the addition of nutrients to food;<sup>32</sup> these were drawn from joint policy statements of the *Food and Nutrition Board* and *Council on Foods and Nutrition of the American Medical Association* as enunciated in 1968<sup>33</sup> and 1973.<sup>34</sup> The FDA also proposed steps to "prevent nutrient 'horsepower' races—the essentially useless addition of nutrients to a food to give a false appearance of nutritional superiority."<sup>35</sup> As before, industry and public opposition to the FDA's proposed regulations was considerable, primarily because of constraints on the marketing and manufacture of dietary supplements.

In 1976, Congress overruled the FDA's regulatory efforts with the passage of the *Vitamins and Minerals Amendments*. The new law stated "the Secretary may not classify any natural or synthetic vitamin or mineral (or combination thereof) as a drug solely because it exceeds the level of potency which the Secretary determines is nutritionally rational or useful."<sup>30</sup> The FDA had failed in its efforts to use "scientific" principles to tightly regulate activities that contributed to what the FDA viewed as needless and irrational consumption of added vitamins and minerals.<sup>30</sup>

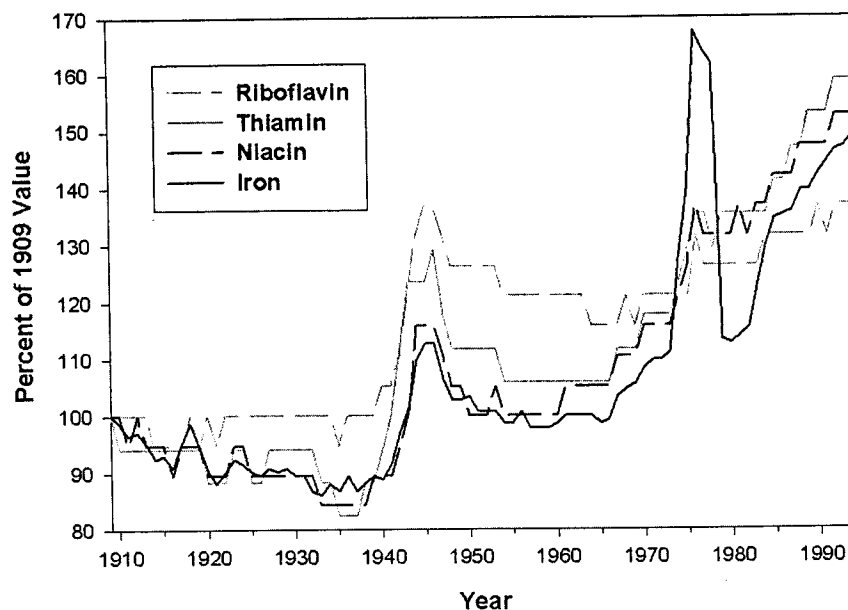
### **New Fortification Policies Based on New Realities**

In 1980, the FDA published its final policy statement on food fortification, and emphasized that "FDA policy continues to be that current nutrition surveys show that widespread fortification of food is unnecessary. . . food fortification should provide consumers with a reasonable benefit without contributing to nutritional imbalance in the diet and without misleading consumers into believing that the consumption of a fortified food per se will ensure a complete or nutritionally sound diet."<sup>36</sup>

However, the new policies reflected the limits placed on the FDA by the *Vitamins and Minerals Amendments*, and were "expressed as a *series of guidelines* [italics added] which manufacturers are urged to follow. . . it is not intended to encourage widespread nutrient fortification of foods."<sup>36</sup> These 1980 guidelines remain the FDA's definitive statement on food fortification to date.

Currently, the FDA endorses the addition of nutrients to foods under four conditions, three of which were either explicitly or implicitly formulated in the 1940s:

- *Nutritional deficiency*: fortification is appropriate if "sufficient information is available to identify the nutritional problem and the affected population groups, and the food is suitable to act as a vehicle for



**Figure 1.** Change in the per capita riboflavin, iron, niacin, and thiamin content of the U.S. food supply between 1909 and 1994.<sup>38</sup> Federally regulated fortification of cereal grain products began in 1941. The nutrient content of the standards of identity was increased in 1973. The levels of iron in cereal grain products were adjusted three times between 1973 and 1981.

the added nutrients.”<sup>36</sup> This policy covers additions to dietary staples such as enriched flour. Manufacturers are “urged to contact the Food and Drug Administration before implementing a fortification plan based on this principle.” Curiously, current policy does not specify that deficiencies be present in “a significant number of people” as recommended by the Food and Nutrition Board.<sup>34</sup>

- *Restoration of nutrient losses:* fortification may be appropriate to replace nutrient losses owing to storage, handling, or processing if losses amount to at least 2% of the U.S. RDA. Much of the original rationale for fortifying flour was to replace industrial losses of nutrients.
- *Improving the quality of a replacement food:* fortification of a food may be appropriate if that food replaces a traditional food of superior nutritional quality. The original rationale for fortifying margarine with vitamin A was to make the manufactured food nutritionally equivalent to butter.
- *Balance nutrient content of food:* fortification of a food may be appropriate if “a normal serving” of the food contains at least 40 kcal (2% of 2000 kcal). The intention of this policy is to provide guidance for “fabricated foods that replace large proportions of the total diet.”<sup>36</sup> The FDA endorses a standard profile of 22 nutrients for addition to these new foods.

Additionally, FDA policy endorses additions of nutrients only if the nutrient is stable under customary conditions, physiologically available, will not result in an excessive intake of the nutrient, and is suitable for its intended purpose.<sup>36</sup>

### Current FDA Regulatory Power

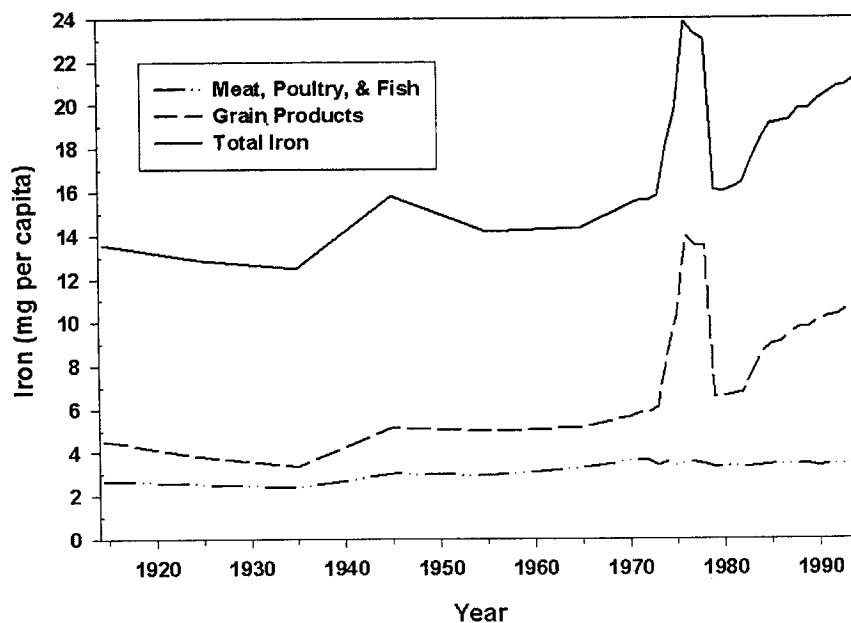
In October 1994, Congress further restricted FDA power to regulate the vitamin and mineral market by passing the *Dietary Supplement Health and Education Act* into law. Under current regulations, the food and supplement industries are provided wide latitude in “structure/function” claims such as “calcium builds strong bones” and “helps maintain cardiovascular health.” Manufacturers of fortified foods are permitted the same “structure and function” claims as dietary supplements.<sup>37</sup>

Because FDA fortification principles are guidelines, the agency has few means of enforcing scientifically based food fortification. Essentially, the FDA must rely on three approaches to limiting additions of nutrients to foods: by establishing standards of identify for particular classes of foods, regulating false or misleading health claims on food packaging (focusing mostly on claims of disease prevention), and intervening in the case of a well documented health problem. Additionally, the Federal Trade Commission regulates false or misleading advertising.

### Current Public Health Issues and Food Fortification

#### *The Nutrient Content of the U.S. Food Supply*

Individual nutrient intakes in the United States are strongly affected by food fortification. As was intended, fortification in the mid-1940s sharply increased the amounts of niacin, riboflavin, thiamin, and iron in the food supply (Figure 1).<sup>38</sup> The greatest increases in these micronutrients, however, have occurred since 1960 ow-



**Figure 2.** Per capita iron in the U.S. food supply from grain cereal products and meat, poultry, and fish.<sup>38</sup> Federally regulated iron fortification began in 1941. The iron content of enriched flour was substantially increased in 1973, a policy that was reversed in 1978 owing to concerns about iron overload. In 1981, the iron content of enriched flour was increased by approximately 25% to simplify manufacture of white bread. In 1994, cereal grain products provided more than 50% of iron in the U.S. food supply.

ing to the combined actions of the food industry and government.

In 1973, the FDA modestly increased the niacin, riboflavin, and thiamin added to cereal grain products in response to recommendations by industry and the *White House Conference on Food, Nutrition and Health*.<sup>39</sup> At the same time, the FDA more than doubled the iron content of enriched flour (from 13–16.5 mg/lb to 40 mg/lb).<sup>40</sup> Later, the FDA reversed itself (in 1978), and returned iron fortification to its pre-1973 levels owing to concerns about iron overload.<sup>41</sup> In 1981, the FDA changed course yet again, and effectively increased iron fortification by eliminating maximum and minimum iron values, and adopting a single iron level (20 mg/lb) for enriched and self-rising flour.<sup>42</sup> Figure 2 shows these two sharp increases in the iron content of U.S. food. The most recent food supply analyses (for 1994) showed the amounts per capita of iron, thiamin, niacin, and riboflavin in the U.S. food supply were approximately 50% above prefortification levels and still rising.<sup>38</sup>

### Industry-initiated Fortification

Although federal food fortification polices have contributed greatly to the changing nutrient profile of the U.S. food supply, much is attributable to foods without standards of identity. Few researchers have examined the contribution of industry-initiated fortification to the national nutrient supply. One of the few studies on the topic showed fortified foods contributing on average 25% of

thiamin, 16% of iron, 13% of niacin, 11% of riboflavin, and 6% of vitamin A consumed by upstate New York women.<sup>43</sup> Foods lacking standards of identity contributed 10% of thiamin, 9% of vitamin C, 9% of iron, 9% of niacin, 8% of riboflavin, and 6% of vitamin A. The biggest “unregulated” contributors of fortified nutrients were breakfast cereals and vitamin C-fortified drinks.

Ready-to-eat cereals are perhaps the biggest single class of food contributing to national micronutrient intakes. In 1969, just 14% of ready-to-eat cereals were fortified.<sup>44</sup> By 1979, after passage of the *Vitamins and Minerals Amendments* (1976), 92% of ready-to-eat breakfast cereals were fortified.<sup>44</sup> Many of these products now contain 100% of the Reference Daily Intake values of several vitamins and minerals. Based on data from the 1989–91 *Continuing Survey of the Food Intakes of Individuals*, ready-to-eat cereals are the top food source of many vitamins and minerals, and a major contributor of several other micronutrients (Table 1).<sup>45,46</sup> Interindividual variation in diets means that some persons have much higher intakes of nutrients from ready-to-eat cereals.

Dietary supplements provide a second unregulated source of vitamins and minerals. In 1997, sales of dietary supplements were estimated as yielding \$12.7 billion, a 13% increase over 1996.<sup>47</sup> The *Third National Health and Nutrition Examination* survey showed nearly half the U.S. population (46%) taking a vitamin or mineral supplement at least once per year, and a quarter of

**Table 1.** The Contribution of Ready-to-Eat Cereals to U.S. Vitamin or Mineral Intakes (1989–1991 CSFII)

	Children (2–18 years old)	Adults
Vitamin A	21.9%	12.0%
Vitamin C	9.8%	4.5%
Folate	30.0%	19.0%
Thiamin	—	12.2%
Riboflavin	—	29.8%
Niacin	—	26.7%
Vitamin B <sub>6</sub>	—	14.6%
Vitamin B <sub>12</sub>	—	8.6%
Iron	26.5%	18.6%
Zinc	10.6%	8.4%

The figures are based on the sum of nutrient intakes across all subjects, and can be interpreted as the nutrient content of that portion of the food supply that is actually consumed by the U.S. population. Source: references 45 and 46.

individuals (24%) reporting daily use of supplements.<sup>48</sup> In 1991, more than half of American preschoolers (54.4%) received a vitamin or mineral supplement at least 3 times per week.<sup>49</sup>

### **Iron Fortification, Anemia, and Hemochromatosis**

Between 1965 and 1994, the total iron in the U.S. food supply increased by substantial amounts (Figure 2). However, total iron intake masks consumption of a range of iron compounds with widely varying bioavailability. In the United States, the two most commonly used iron fortificants are ferrous sulfate, which is mostly added to bakery and pasta flour and infant formulae, and elemental iron (which includes carbonyl, electrolytic, and reduced iron). Ferrous sulfate is water-soluble and is highly bioavailable.<sup>50</sup> By contrast, elemental iron is water-insoluble and much less bioavailable.<sup>51</sup> Using ferrous sulfate as a reference with a relative bioavailability (RBV) of 100%, the bioavailability of elemental iron can range from 5% to 20% when consumed in a meal, and up to 70% when consumed alone in high doses.<sup>52,53</sup> Rates of absorption depend on a range of factors, including the composition of the meal, the physicochemical aspects of the fortificant, and the iron status of the individual.<sup>50,51</sup>

From the standpoint of deficiency, additional iron in the food supply has been an apparent success. The prevalence of anemia substantially decreased in the 1970s and 1980s. In six states, rates of anemia among low-income children declined by approximately 50% between 1976 and 1985.<sup>54</sup> In a middle-class Minnesotan population, childhood iron deficiency anemia was essentially eliminated.<sup>55</sup> Although several factors contributed to this improvement, particularly federal food programs such as the *Women, Infants and Children* program, some

unknown portion of the declining prevalence of iron deficiency anemia can be attributed to increased iron fortification. Today, nationally representative data suggest the prevalence of iron deficiency anemia in the United States to be just 3% for toddlers, 2% for adolescent girls, and 5% for women of childbearing age; this amounts to approximately 240,000 toddlers and 3.3 million women.<sup>56</sup> Despite these advances, subpopulations with much higher rates of anemia exist in parts of the United States, particularly among the poor and non-white.<sup>57</sup>

From the perspective of iron toxicity, high levels of iron fortification have the potential to be harmful. Risk of iron overload occurs because humans have no biologic mechanism for excreting excess iron. Protection from toxicity occurs by tight regulation of iron absorption; recent research shows adequate-to-high iron status (serum ferritin 20+  $\mu\text{g/L}$ ) in most men is associated with poor bioavailability of both heme and nonheme iron.<sup>58,59</sup> As a result, levels of iron absorption in the iron-replete individual approximate basal requirements. Therefore, the normal individual should be protected against iron overload, regardless of the level of iron fortification.

One subgroup of the population is nevertheless at risk of iron overload: middle-aged adults with the autosomal recessive condition known as hereditary hemochromatosis. Recently, the genetic basis of the disorder was clarified when two alleles for a single gene were found to be associated with an estimated 60 to 90% of hemochromatosis cases.<sup>60</sup> When homozygous for these alleles, iron absorption occurs efficiently despite high iron stores. Without an effective mechanism for reducing iron absorption, the metal accumulates in the body tissues, leading to morbidity and death.

In the United States, an estimated 2 to 5 adults per 1000 are homozygous for the hemochromatosis alleles,<sup>61</sup> which translates into as many as 1 million persons at risk of iron overload. Because of under-reporting and low awareness of the condition, the prevalence of hemochromatosis-related death and illness in the United States remains poorly established. An estimated 50% of males and 25% of females with the homozygous condition are thought to be at high risk of serious complications,<sup>62</sup> particularly white men age 40 and older, and women over the age of 50.<sup>63</sup>

From 1979 to 1992, age-adjusted rates of hemochromatosis-related deaths increased by 60%, resulting in nearly 5000 reported deaths during the time period.<sup>63</sup> Although methodological issues may have contributed to the apparent increase in mortality, the trend is also consistent with steadily increasing iron in the food supply.

A related risk of iron fortification occurs owing to iron's capacity to generate free radicals. In the early

1980s, Sullivan hypothesized a causal relationship between high iron stores and coronary heart disease based on this premise.<sup>64</sup> A decade later, researchers in Finland observed an association between high levels of serum ferritin and risk of myocardial infarction, which raised the specter of widespread iron toxicity.<sup>65</sup> Subsequent epidemiologic research has largely rejected an association between ferritin and heart disease.<sup>66,67</sup> However, the Finnish research group continues to observe associations between iron status and coronary heart disease.<sup>68,69</sup> Even if unrelated to heart disease, the pro-oxidant capacities of iron have made it a suspect in a variety of disease conditions.<sup>70</sup> Perhaps most provocative are reported associations between colorectal cancer and iron, because any causal effect, if established, might occur without the necessity of iron absorption.<sup>71,72</sup>

### **Folate and Neural Tube Defects**

In 1974, the Food and Nutrition Board recommended that folate plus calcium, magnesium, zinc, vitamin A, vitamin B<sub>6</sub>, and the "basic four" (i.e., riboflavin, niacin, thiamin, and iron) be added to all cereal grain products.<sup>73</sup> The "10-nutrient proposal" was evaluated for feasibility and effectiveness by the cereal industry and found to be generally feasible, but the proposal was never implemented.<sup>44,74</sup> More than 20 years later in 1996, the FDA added folate to the standards of identity for enriched breads, flours, corn meals, pastas, rice, and other grain products (effective January 1, 1998).<sup>75</sup> As a result, folate joined the "basic four" first added to grain products in the 1940s.

The 1996 addition of folate to grain products was prompted by clinical trials that showed significant reductions in the risk of neural tube defects (NTD) among infants whose mothers had been supplemented with folic acid. Folate fortification followed a 1992 Centers for Disease Control recommendation that "all women of childbearing age in the United States who are capable of becoming pregnant should consumed 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected by spina bifida or other NTDs."<sup>76</sup>

In the United States, NTDs affect an estimated 4000 pregnancies and 1500 live births per year, and NTDs are a major contributor to infant mortality, comprising approximately 1.3% of infant deaths.<sup>77,78</sup> The medical costs for treating U.S. children with NTDs are estimated to exceed \$200 million per year.<sup>79</sup> Because NTDs occur very early in pregnancy (17–30 days of gestation), and 50% of U.S. pregnancies are unplanned, public health interventions must target women who are not yet pregnant and who may not plan to become pregnant. Additionally, 95% of NTDs are born to couples with no family history of the disorder. For these reasons, the FDA viewed fortification, a "passive" public health intervention, as the best approach to preventing NTDs.<sup>75</sup>

The FDA "estimated that . . . 116 NTDs per year would be prevented" plus an additional 25 infant deaths per year by fortifying grain products with folate.<sup>75</sup>

Despite its potential benefits, folate fortification represented a major shift in longstanding public health policies that had emphasized the necessity of widespread nutrient deficiency in a well defined segment of the population as a prerequisite for fortification. Instead, folate fortification targeted a small, ill-defined population, while exposing 260 million Americans to higher levels of the vitamin. Moreover, simulations suggested that the added folate would disproportionately increase intakes among those least in need of folate, while increasing risk of adverse effects from undetected vitamin B<sub>12</sub> deficiency in the elderly.<sup>80,81</sup> To reduce risk of the latter, the FDA adopted a lower folate fortification level than advocated by some, and restricted fortification to a few staple foods. Additionally, the FDA adopted policies to discourage indiscriminate folate fortification by manufacturers.<sup>75</sup> Nevertheless, the agency's decision to fortify cereal grains with folate has been controversial.<sup>82,83</sup>

In its deliberations, the FDA recognized a second potential benefit of folate fortification: a possible decline in rates of cardiovascular disease.<sup>75</sup> Many observational studies have shown associations between elevated homocysteine levels and risk of cardiovascular disease.<sup>84</sup> The FDA considered the link between homocysteine and cardiovascular disease to be preliminary, however, and an insufficient basis for folate fortification. With respect to children, recent research has identified associations between hyperhomocysteinemia and a range of poor birth outcomes other than NTDs, including early pregnancy loss, limb deformities, and congenital heart defects.<sup>85</sup> If homocysteine proves to be a causal agent in a wide variety of disorders, then the FDA's narrowly based decision to fortify cereal grains with folate may have a much broader range of benefits, which should make folate fortification more acceptable to those who felt the new FDA policy exposed too many to risk and benefited too few.

Since the FDA decision, new scientific research has focused on NTDs and genetic variability in B vitamin metabolism. In 1995, Van der Put et al.<sup>86</sup> identified an association between NTDs and a common polymorphism (677C → T) of the gene encoding methylenetetrahydrofolate reductase (MTHFR). The conversion of homocysteine to methionine is dependent on the presence of a methyl donor (5-methyltetrahydrofolate), which is provided by the action of MTHFR. Individuals who are homozygous for the 677C → T polymorphism have substantially reduced enzyme function, which can lead to elevated homocysteine levels.<sup>87</sup> Because higher folate intakes compensate for impaired enzyme activity, these individuals have functionally higher folate requirements.

at least with respect to methylation capacity and homocysteine.

The work of the Dutch group has prompted additional research on the relationship of the 677C → T polymorphism to NTDs. The results of these investigations have been decidedly mixed, however, perhaps owing to small sample sizes and differences in populations and nutritional status.<sup>88,89</sup> Other research has examined the relationship of MTHFR polymorphisms to cardiovascular disease and cancer.<sup>87,90</sup> Additionally, researchers have examined several other genetic polymorphisms that might influence homocysteine metabolism and lead to increased risk of health problems, including variants of methionine synthase, methionine synthase reductase, and cystathionine β-synthase.<sup>91,92</sup> Although the role of MTHFR 677C → T and other genetic polymorphisms in the etiology of NTDs remains unclear, the research has demonstrated considerable genetic variability in B vitamin metabolism and, therefore, in nutritional requirements.

### Looking to the Future: Public Health Issues Related to Food Fortification

#### **Food Fortification, Emergent Deficiencies, Growth, and Development**

In 1941, large segments of the U.S. population were demonstrably malnourished. Classic techniques such as depletion-repletion studies, based on relatively small numbers of subjects, provided the basic information needed to estimate average nutritional requirements to prevent deficiency syndromes; many of these same early studies continue to provide a basis for the new DRI values.<sup>93</sup> Based on clear need, food fortification programs were designed that benefited large numbers of people.

In the 1990s, the nutritional situation in the United States is profoundly different than 5 decades ago. The classic deficiency syndromes, with the exception of iron deficiency anemia, have been virtually eliminated as a result of food fortification (both private and government sponsored), nutrition education, and a steady decline in the cost of food relative to income. The classic nutrient deficiencies have been supplanted in the United States by "emergent deficiencies," a term coined by Pelletier and Habicht that:

"refers to nutrients or food components that were not recognized as a problem in the past, but which new evidence suggests may be a problem. Examples include folate and neural tube defects, zinc and child growth, selenium and cancer, potassium and hypertension, antioxidants and cardiovascular disease, iron deficiency and lead toxicity, etc."<sup>94</sup>

As opposed to the apparently more mechanistic classic deficiencies, the effects of the emergent deficiencies

are generally of a statistical nature, involving differences in levels of risk. In a generally well nourished population, the probabilistic quality of the emergent deficiencies presents a very different set of policy issues than existed in the 1940s, as indicated by the controversies surrounding folate and iron fortification.

#### **Risk of Nutrient Deficiency in Well Nourished Populations**

From a public health perspective, food fortification should serve the nutritional needs of the population. Within this framework, fortification policies should be judged on whether the health and function for the population is improved or harmed. Because actions that are beneficial to the child (suffering from iron deficiency anemia) may prove damaging to the adult (possessing hereditary hemochromatosis), careful attention should be paid to understanding the tradeoffs involved. A number of factors must be assessed in such a cost-benefit analysis; among these is a consideration of the distribution of individual nutrient requirements.

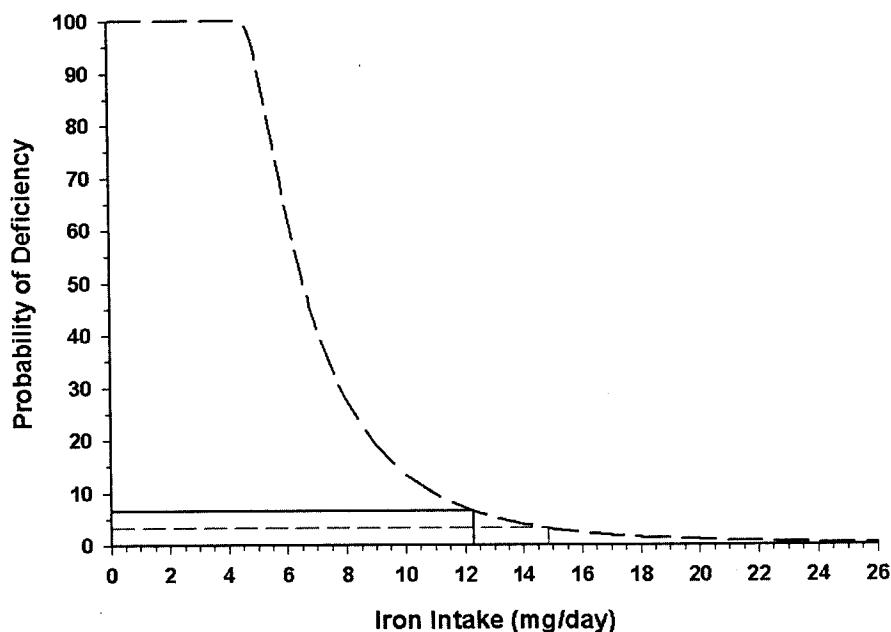
Figure 3 plots risk of iron deficiency in menstruating women given a plausible distribution of requirements as published by the Food and Nutrition Board,<sup>95</sup> and illustrates an important feature of food fortification in generally well nourished populations. Intuitively, very low nutrient intakes result in a 100% chance of deficiency, whereas very high intakes signify negligible risk. At intermediate intakes, risk of deficiency is a complex function of the distribution of requirements. Consider the hypothetical situation in which all women consume 12.3 mg of iron per day (the U.S. national average for women aged 20–59).<sup>48</sup> In this generally well nourished population, the predicted prevalence of iron deficiency would be approximately 6.7%, and all deficiency would be restricted by definition to those few women with the very highest iron requirements. Because these women fall in the tail of the distribution, a modest increase in nutrient intakes would result in very small declines in the prevalence of deficiency. In fact, a 50% reduction in the prevalence of iron deficiency would require increasing everyone's iron intakes by 2.6 mg per day (or 21%).

Focusing on risk of deficiency, the following can be proposed for a generally well nourished population:

- Deficiency will disproportionately be borne by those with the highest nutrient requirements—those in the tail of the distribution. MTHFR polymorphisms and NTDs likely provide an example of this situation.
- Each increase in the food supply's nutrient content will yield diminishing returns in reduced rates of nutrient deficiency.

Analogously, risk of toxicity will be borne disproportionately by those who are most susceptible to high intakes (e.g., hereditary hemochromatosis), and each unit increase in the nutrient content of the food supply will be





**Figure 3.** Probability of iron deficiency in menstruating women for different levels of iron intake. The curve assumes a log-normal distribution of iron requirements, and is based on a model proposed by the Subcommittee on Criteria for Dietary Evaluation of the Food and Nutrition Board.<sup>96</sup> The solid black line indicates probability of iron deficiency with an iron intake of 12.3 mg/day. To decrease the risk of deficiency by 50% (grey dashed line) would require an iron intake of 14.9 mg/day.

accompanied by acceleration in the prevalence of toxicity. The risk and benefit of food fortification would be a function of the distribution of nutritional requirements and susceptibility to toxicity, neither of which are well characterized for most nutrients.

Nutrient intake is the second major parameter affecting nutritional status. Nutrient intakes are highly variable and strongly influenced by a wide range of socioeconomic and other factors. Food fortification is an important technique for improving the nutritional status of low-income populations and other groups at nutritional risk. The effectiveness of the fortification program would depend on the groups' nutrient intakes with respect to the distribution of nutrient requirements and the characteristics of the food vehicle. If the average nutrient intake of the subpopulation falls near the tail of requirement, and the food vehicle is untargeted, then a large proportion of the population will be exposed to increased nutrient intake for relatively little decrease in the prevalence of deficiency. On the other hand, a targeted food such as corn tortillas or special breakfast cereals might substantially reduce risk of deficiency while minimizing risk of toxicity in the greater population.

### **The Food Industry and Scientifically Based U.S. Food Fortification**

In the 1960s, the FDA suffered the first of a series of defeats in its attempts to regulate indiscriminate food fortification. Today, federal regulation of food fortification has nearly returned to the pre-1938 situation. Juice drinks are fortified with  $\beta$ -carotene, tortilla chips with

lutein, and breakfast cereals with 100% of the RDA of a wide variety of vitamins and minerals. With the major exception of the ability to remove dangerous products from the market and to regulate health claims on labels, the FDA has little authority to regulate industry-sponsored fortification. Not coincidentally, the nutrient content of the U.S. food supply has increased steadily since the 1960s, and much of this has occurred via essentially unregulated food fortification. With increasing ability to detect relatively subtle or uncommon effects owing to marginal malnutrition, the nutritional sciences create a new frontier for food fortification. The public health significance of these scientific advances should be assessed within the context of a population that is generally well nourished. These changes will present new challenges for public health professionals, the FDA and food fortification policy.

With increasing information on nutrient requirements, the distribution of those requirements and the functional effects of malnutrition, the potential to craft fortification policies that maximize benefits and minimize risk should be enhanced. This new knowledge may provide a basis for renewed federal regulation of food fortification based on endangerment to the public's health. In the case of iron, several thousand persons have died from hemochromatosis in the past decade. Industry-initiated additions of iron to the U.S. food supply may have contributed to a problem that is much more prevalent than NTDs. Scientifically based food fortification offers the possibility of better health and performance,

but perhaps only by restraint of currently unregulated fortification.

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