

## Fortification: new findings and implications

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*This article reviews the current landscape regarding food fortification in the United States; the content is based on a workshop sponsored by the North American Branch of the International Life Sciences Institute. Fortification of the food supply with vitamins and minerals is a public health strategy to enhance nutrient intakes of the population without increasing caloric intake. Many individuals in the United States would not achieve recommended micronutrient intakes without fortification of the food supply. The achievement and maintenance of a desirable level of nutritional quality in the nation's food supply is, thus, an important public health objective. While the addition of nutrients to foods can help maintain and improve the overall nutritional quality of diets, indiscriminate fortification of foods could result in overfortification or underfortification in the food supply and nutrient imbalances in the diets of individuals. Any changes in food fortification policy for micronutrients must be considered within the context of the impact they will have on all segments of the population and of food technology and safety applications and their limitations. This article discusses and evaluates the value of fortification, the success of current fortification efforts, and the future role of fortification in preventing or reversing nutrient inadequacies.*

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### INTRODUCTION

In the current environment of overconsumption in the United States, in which caloric intakes exceed energy expenditure, it is a matter of concern that intakes of some micronutrients are substantially below recommendations. Because the 2010 US Dietary Guidelines for Americans (DGAs) recommend that consumers “control total calorie intake to manage body weight,”<sup>1</sup> there is a renewed focus on meeting micronutrient needs while staying within calorie limits. With respect to fortification in developing countries, the World Bank stated that “prob-

ably no other technology available today offers as large an opportunity to improve lives and accelerate development at such low cost and in such a short time.”<sup>2</sup> The benefits of fortification are also substantial in more highly industrialized countries.

In 1987, the Codex Alimentarius Commission outlined general principles for adding nutrients to foods.<sup>3</sup> It used the terms “fortification” and “enrichment” interchangeably, with the following definition: “Fortification or enrichment means the addition of one or more essential nutrients to a food whether or not it is normally contained in the food for the purpose of preventing or

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**Table 1 Examples of foods with standards of identity and nutrient levels for enriched cereal grains.**

Enriched grain products	Thiamin (mg/lb)	Riboflavin (mg/lb)	Niacin (mg/lb)	Iron (mg/lb)	Folic acid (mg/lb)
Breads, rolls, buns	1.8	1.1	15	12.5	0.43
Corn meal	2–3	1.2–1.8	16–24	13–26	0.7–1.0
Farina	2–2.5	1.2–1.5	16–20	≥13	0.7–0.87
Flour	2.9	1.8	24	20	0.7
Macaroni and noodle	4–5	1.7–2.2	27–34	13–16.5	0.9–1.2
Rice	2–4	1.2–2.4	16–32	13–26	0.7–1.4

Adapted from the US Food and Drug Administration 21CFR104.20 (1977).<sup>5</sup>

correcting a demonstrated deficiency of one or more nutrients in the population or specific population groups.”

In the first half of the 20<sup>th</sup> century, fortification was used to address classical nutrient deficiencies throughout the world. In the United States, iodine was added to salt to reduce the risk of goiter; vitamin D was added to milk to reduce the risk of rickets; and iron, thiamin, niacin, and riboflavin were added to wheat flour and other cereal products to replace nutrients lost during the milling process and to reduce the risk of iron-deficiency anemia, beriberi, pellagra, and riboflavin deficiency, respectively.<sup>4</sup> For cereal grains in the United States, although the levels of nutrients mandated originally were set to replace losses in processing rather than to increase nutrient levels, the intent was the same, i.e., to add specific nutrients to foods that were frequently consumed to ensure nutrient adequacy in the American population.<sup>5</sup> Folic acid was included in the US Food and Drug Administration (FDA) standards of identity for enriched grain-based foods in the 1990s to reduce the risk of neural tube defects (NTDs).<sup>6</sup> For some foods, such as enriched flour and bread, standards of identity specify the nutrients and the levels of those nutrients that must be added (Table 1). Fortified and enriched foods help to improve the overall nutritional quality of the food supply and address a demonstrated public health need.

The FDA published its food fortification policy in a 1980 document entitled “Nutritional Quality of Foods; Addition of Nutrients.”<sup>7</sup> The policy’s objective was to establish a uniform set of principles and guidelines that would serve as a model for the rational addition of essential vitamins and minerals to food. That policy remains in effect today. The FDA considers only those essential vitamins and minerals that are listed as reference daily intakes (RDI) under the Code of Federal Regulations 21, Section 101.9 on the Nutrition Labeling of Food, as well as protein, to be within the scope of its fortification policy.<sup>8</sup> FDA’s fortification policy provides guidance on when it is appropriate to add nutrients to foods (e.g., restoration; correcting dietary insufficiency; avoiding nutritional inferiority; maintaining a balanced nutrient profile in a food like a meal replacement). FDA’s fortification policy focuses on restoring nutrients to levels representative of

the food prior to storage, handling, and processing; obtaining sufficient information to identify the nutritional problem and the affected population group; determining if the food chosen for fortification is a suitable vehicle for the added nutrient(s); correcting a dietary insufficiency recognized by the scientific community and known to result in dietary deficiency disease or a public health-related problem; maintaining a balanced nutrient profile in proportion to the caloric value of a food; and improving the quality of a replacement food so as to avoid nutritional inferiority relative to the food it replaces.

Nutrients added to foods must be approved food additives or must be categorized as generally recognized as safe under conditions of their intended use. It is important that nutrient fortification is appropriate and necessary. The fortification of fresh produce, meat, poultry or fish products, sugars, or certain snack foods (e.g., candies or carbonated beverages) and the indiscriminate addition of nutrients to foods are all deemed to be inappropriate.

Some nutrients, such as folic acid and vitamin D,<sup>9</sup> are specifically limited by regulations regarding which foods can be fortified, and at what levels, to avoid overconsumption. In contrast, vitamin A can be added to any food without limitation, other than those imposed by good manufacturing practices. Margarine is required to contain vitamin A and may contain vitamin D.<sup>10</sup> Whole milk may be fortified with vitamin A at a level not less than 500 IU per 8-oz serving and vitamin D to a level of 100 IU per 8-oz serving, which reflect 10% and 25% of the daily value (DV), respectively.<sup>11</sup> Reduced-fat milks must be fortified with vitamin A to avoid nutritional inferiority. Although fortification of milk with vitamin D is voluntary in the United States, nearly all pasteurized fluid milk sold in the United States contains added vitamin D.

Before the FDA mandates fortification of the food supply with a nutrient, the agency performs a dietary modeling exercise of current dietary intakes to evaluate possible fortification levels for the target population that will be effective and simultaneously maintain a safe level of intake for the nontarget population. The most recent example of an addition to the FDA’s fortification policy, based on public health concerns, was the FDA’s final ruling in 1996 on the addition of folic acid to enriched

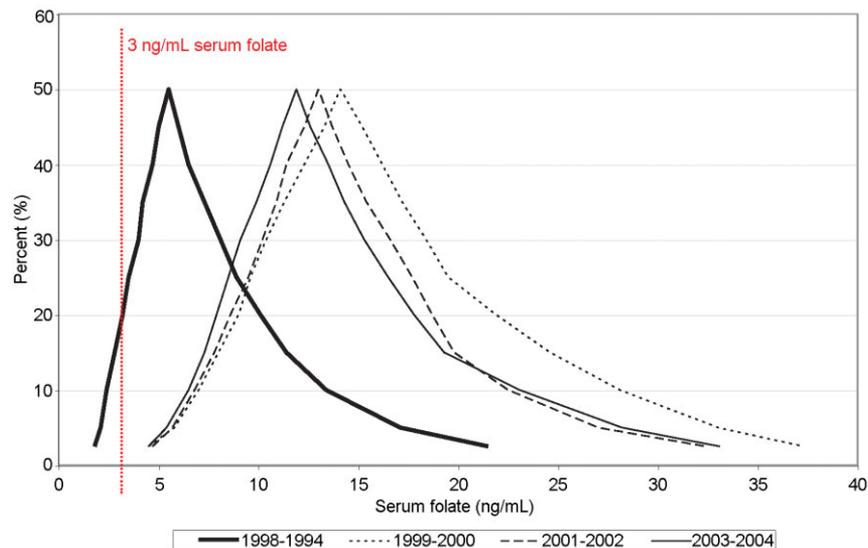


Figure 1 Trends in serum folate, before and after folic acid fortification in the United States. Adapted from Pfeiffer et al.<sup>16</sup>

grain products to reduce the risk of NTDs.<sup>6,12</sup> The change in policy was in response to the 1992 recommendation from the US Department of Health and Human Services Public Health Service and Centers for Disease Control that all women of childbearing age capable of becoming pregnant consume 400  $\mu\text{g}$  of folic acid daily.<sup>13</sup> The rationale for fortifying cereal grains was that they are consumed by 90% of women<sup>6</sup> and their fortification would increase the folic acid intake of most women of childbearing age without requiring a change in dietary patterns of the target population. Canada also has mandatory folic acid fortification. As reported in 2011, although less than 1% of Canadians are folate deficient and 40% show high red blood cell folate concentrations ( $>1,360$  nmol/L), almost one-quarter of women of childbearing age have suboptimal folate concentrations for maximal NTD risk reduction.<sup>14</sup> Before the decision was made to fortify enriched grains with folic acid in the United States, the FDA estimated the effects of fortification on the population.<sup>6</sup> Estimated distributions of current total daily folate intake from a national food consumption survey<sup>15</sup> were created for eight age groups for males and females, including intake from dietary supplements. The increase in folic acid intake was projected for various food fortification options, including enriched cereal grains at 70, 140, and 350  $\mu\text{g}$  of folic acid per 100 g, and breakfast cereal at 100 or 400  $\mu\text{g}$  folic acid per serving. Based on the exercise, folic acid fortification was approved for enriched grains as well as breakfast cereals, corn grits, meal replacement products, infant formula, and foods for special dietary use. As a result of the change in folic acid fortification policy, there has been an increase in folic acid intake and an improvement in folate status (serum and red blood cell folate

levels) as well as a reduction in the prevalence of NTDs in both the United States and Canada.<sup>16,17</sup> Folic acid fortification occurs in more than 60 countries today.<sup>18</sup> Figure 1 shows trends in serum folate levels before and after fortification in the United States.

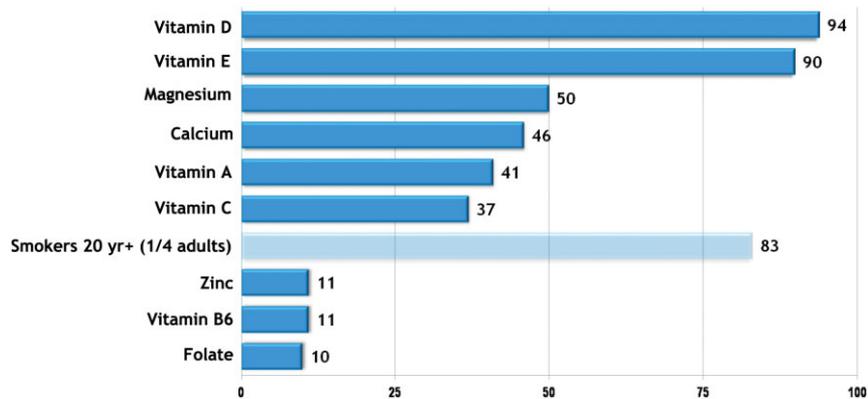
Although nutrient fortification of foods clearly is helpful for alleviating some nutrient deficiencies in the short term, it is not a panacea. Appropriate modeling, testing, and monitoring must be undertaken before fortification is implemented and the underlying causes for specific nutrient deficiencies must ultimately be addressed.

#### NUTRIENT SHORTFALLS IN US DIETS AND IMPACT OF FORTIFICATION

In the latter part of the 20<sup>th</sup> century, analyses of food sources of nutrients showed that in national surveys, fortified foods like enriched grain foods and ready-to-eat cereals were major contributors to intakes of some nutrients.<sup>19–21</sup>

The 2010 DGAs identified several nutrients of concern that were low in diets consumed by many Americans; these included potassium, dietary fiber, calcium, and vitamin D in the general population, and iron, folate, and vitamin B<sub>12</sub> in certain subpopulations.<sup>1</sup>

Population-based surveys are useful for monitoring nutrient intakes and identifying shortfalls and excesses in the US population. To identify sources of the nutrients of concern and 15 other nutrients in the adult American diet, the North American branch of the International Life Sciences Institute (ILSI) sponsored a modeling exercise. In this exercise, data from the 2003–2006 National Health and Nutrition Examination Survey (NHANES) was used



**Figure 2 Percentage of Americans with usual intakes from food below their estimated average requirements.** Data are from *What We Eat in America, NHANES 2005–2008*, for individuals aged  $\geq 1$  year, excluding breastfed children and pregnant or lactating females, except where noted, using the National Cancer Institute’s method for usual intake estimation. Adapted from the US Department of Agriculture.<sup>22,23</sup>

to assess the contributions of micronutrients to usual intakes derived from all sources categorized as follows: foods in which the nutrients naturally occur, fortified and enriched foods and beverages, and dietary supplements. The analysis revealed that a significant portion of Americans fell short of the estimated average requirement (EAR) for one or more of these “shortfall” nutrients, even when intakes from dietary supplements were included. An analysis of NHANES 2005–2008 data reported in *What We Eat in America*, which examined intakes only from food, showed similar nutrient shortfalls in the US population (Figure 2).<sup>22,23</sup>

Based on various analyses of NHANES 2003–2008 data, approximately 70–94% of the population was below the EAR for vitamin D, between 38% and almost 50% of the population was below the EAR for calcium, and one-quarter to more than one-third of the population was below the EAR for vitamin C. The range for each nutrient varied by subject age and supplement use.<sup>22–24</sup> For some nutrients, dietary intakes were inadequate only for certain groups, e.g., vitamin B<sub>6</sub> and folate among adult females, phosphorus among teenage girls, zinc among adults aged  $\geq 70$  years and teenage girls aged 14–18 years, and iron among pregnant females.

It is important to examine the proportion of the population with intakes that fall short solely from food sources of nutrients since this reflects intakes from the food supply, as it is today, for those individuals who do not use dietary supplements. Fortification of the food supply is an alternative to relying on supplement use (Figure 2). According to an analysis of the data in *What We Eat in America, NHANES 2003–2006*, many Americans would not have achieved the micronutrient intake levels recommended in the dietary reference intakes (DRIs) without one or a combination of the following: food fortification, food enrichment, and the use of

dietary supplements.<sup>24</sup> Enriched and/or fortified foods contribute a large proportion of the intakes of vitamins A, C, and D, as well as thiamin, iron, and folate, although intakes for some of these nutrients are still below the EAR for a significant portion of the population.<sup>24</sup> Most of the water-soluble vitamins in US diets come from enriched/fortified foods and/or supplements, whereas the major sources of most minerals, with the exception of iron, are foods that are neither enriched nor fortified.<sup>24</sup> It should be noted that vitamin D represents a special case because much of the body’s supplies come from exposure to sunlight rather than dietary sources, thus making diet a poor proxy for nutritional adequacy. An analysis has also been completed of the impact of enrichment/fortification in children.<sup>25</sup>

Examining the degree of conformity to recommended patterns of food consumption is another strategy for monitoring nutrient exposure. The US Department of Agriculture (USDA) Food Patterns are examples of dietary patterns that meet almost all nutrient goals within estimated energy needs. The modern versions of these patterns are designed to help individuals adhere to the recommendations in the DGAs and are the starting point for developing other educational programs and materials, such as those on the ChooseMyPlate.gov website and the USDA’s SuperTracker dietary assessment tool.<sup>26–28</sup> The food patterns describe daily amounts of foods to eat from food groups and subgroups, with emphasis on nutrient-dense foods. The patterns also include an allowance for oils and limited amounts of solid fats and added sugars and other high-calorie, low-nutrient-density foods that can be eaten after fulfilling other parts of the pattern, while keeping within energy needs.<sup>28</sup>

Nutrient adequacy is built into the food patterns and is assessed by using a “nutrient profile” developed for each food group or subgroup. The process for developing these

nutrient profiles involves creating food and ingredient “item clusters” and selecting a food to represent each cluster before calculating a weighted nutrient profile for each group.<sup>26</sup> The choice of the representative food for each cluster is an important determinant of the amounts of nutrients in the patterns; for example, the choice of a fortified product can increase levels of specific nutrients. The first dietary patterns designed to represent a total diet were developed by the USDA in the 1980s. A major revision of the food patterns was completed in 2005 in preparation for the release of the 2005 DGAs. The patterns were again updated and evaluated in 2010 to ensure consistency with the 2010 DGAs. In a limited number of cases for the 2010 DGAs, a fortified food was selected as the representative food for an item cluster in the modeling, such as when fortification levels were mandatory, as with folate in enriched grains, or ubiquitous, as with vitamins A and D in fat-free and low-fat milk. Some fortified foods were also included as representative when they were clearly the market leader and consumption in the population of the food was consistent over time, as with fortified ready-to-eat cereals.<sup>28</sup> Most nutrient levels in the patterns are at or above their adequacy goals when the patterns are followed.<sup>28</sup> However, the dietary patterns that were developed yielded intakes of potassium, vitamin E, vitamin D, and choline that were less than goal amounts (although they were greater than current intakes). Most nutrients in the dietary patterns come from nonfortified food sources; therefore, it is possible that the dietary patterns supply more than the stated levels for some nutrients if fortified foods are selected.

### **CHALLENGES IN ASSESSING NUTRIENT INTAKES TO DETERMINE EFFECTIVE, YET SAFE, FORTIFICATION**

There are many challenges associated with the assessment of nutrient intakes from foods and supplements in order to predict or monitor impacts of fortification. It is important to deal with these challenges because changes in fortification and in FDA policy could have effects on the nutrition of the population. These changes would likely vary from nutrient to nutrient, food vehicle used, and target group. The impact of any change in fortification policy on individuals will vary according to age, sex, and health status and shifts in dietary patterns that occur over time. Ideally, the foods that are selected for fortification are critical because they must reach the high-risk portion of the population to enhance their intakes without creating excessive intakes for the rest of the population.

If a single food is fortified, it is not certain that everyone will benefit because some may not consume that food for one reason or another; this is true with vitamin D-fortified milk, which is often avoided by those who believe they are allergic or intolerant to milk. In addition,

it is possible that fortification may miss the intended population because individuals consuming the poorest diets may be less likely to eat the fortified foods. Although fortification shifts nutrient intakes for everyone who consumes the fortified food, and not just the target population, those who do not include the food in their diets will not benefit. Fortification of a staple food or food component will increase the consumption of the nutrient, but it will occur at a differential rate for low and high consumers of that item. Fortifying several foods or ingredients used in many foods with a single nutrient may benefit a larger number of people, but it becomes more difficult to assess the impact of fortification on the population and to avoid excessive intakes among heavy consumers of fortified foods in general. However, with respect to the United States, a recent population-based survey found that the percentage of individuals exceeding the tolerable upper intake level (UL) for most nutrients (calcium, iron, zinc, and vitamins A, C, and E), including food and supplements, was relatively small.<sup>24</sup>

### **Consumer understanding**

In addition to increasing nutrient intakes within the population to varying degrees, fortification appears to have an impact on consumers’ purchasing decisions, which can ultimately affect their health and well-being. According to findings of the International Food Information Council’s Food & Health Survey, four out of five Americans purchase foods and beverages specifically because of fortification or another added benefit. About one-third believe that fortification has a moderate or great impact on their overall health. A little more than one-quarter indicated that fortified foods have a great or moderate impact on their food purchasing decisions.<sup>29</sup> The FDA has expressed interest in studying consumers’ understanding of fortification further, with one specific area of interest being beliefs about the degree to which fortified snack foods (such as cookies, candy, and carbonated beverages) can be used as lower-calorie, more nutrient-rich substitutes for other foods and still ensure a nutritionally sound diet.<sup>30</sup>

### **Nutrient intakes**

In population monitoring and surveillance, the goal is to obtain an estimation of usual intakes that reflect long-term chronic exposure to the nutrients in question. Usual intakes are not directly observable and are estimated from short-term, self-reported data, such as two of the *What We Eat in America*, NHANES 24-h dietary recalls for the same individual; these recalls have less systematic error than food frequency questionnaires and are, therefore, more suited to estimating usual nutrient intake distributions.

NHANES provides population-based data for estimating nutrient shortfalls and excesses within the US population, and such information is essential for establishing and evaluating fortification policy. Food and nutrient intakes normally vary considerably from day to day. In surveys before 2002, most NHANES data were based on single-day 24-h recalls of food, beverage, and self-reported supplement use over the past 30 days, and may thus have overestimated both the number of very low and very high intakes. NHANES data collected after 2002 are based on two separate 24-h food and supplement intake recalls, and give better estimates of the distribution of usual intakes.<sup>31</sup>

If the goal is to obtain group mean intakes of nutrients, nutrient intakes from food and dietary supplements can simply be added and the means calculated. If, however, the goal is to determine inadequacies, excesses, or percentiles of the population at each level of intake, nutrient intake distributions must be adjusted for within-person variability. Within-person variability is needed to monitor the tails at the high and low ends of the distribution curve. With repeated 24-h recalls, day-to-day variability in nutrient intakes can be decreased and estimates of the usual intake distribution can be obtained. This method may also account for effects such as day of the week, recall sequence, and interview mode.<sup>32,33</sup>

Monitoring dietary intakes of nutrients is necessary to assess the impact of fortification. However, dietary intakes by themselves are not necessarily representative of nutritional status, or the impacts of inadequacies, or excesses. As a result, FDA fortification regulations are worded in such a way that fortification cannot be based on dietary intake data alone. Decisions regarding fortification are most well supported when they are based on biomarkers of intake and intermediary and ultimate markers of health outcomes as well, although clinically evident differences can be difficult to detect, despite large differences in nutrient intake. NHANES monitors folic acid and its metabolites in the blood, whereas the Centers for Disease Control and Prevention continually monitor the impact of fortification on the incidence of NTDs. The FDA monitors intake and nutritional status, while addressing safety concerns. These observations factor into decisions on whether alterations in folic acid fortification levels are needed.<sup>34,35</sup> However, this approach creates a conundrum for vitamin D because dietary intake is only one source of the vitamin. Thus, although intakes of vitamin D are low for most of the American population, the majority have blood levels of vitamin D that are within established normal levels, suggesting that exposure to sunlight with synthesis of the vitamin in the skin is also a major factor determining nutritional status.<sup>36</sup>

## Dietary supplements

Supplement usage can significantly alter nutrient intake distributions and further complicates the task of estimating nutrient intakes and evaluating the effects of fortification on nutritional status. Only some members of the population use dietary supplements, therefore, their impact on nutrient intakes is limited to that subgroup, whereas most of the population is exposed to fortification and enrichment. Although supplement use increases the percentage of people meeting the EAR, it also increases the percentage that may exceed the UL. Persons who regularly choose enriched/fortified foods and use high-dose dietary supplements may exceed the UL.<sup>24</sup>

About one-half of the adult US population and 70% of adults aged  $\geq 71$  years use dietary supplements.<sup>37</sup> The majority of people report only using one or two dietary supplements on a regular basis. A multivitamin-multimineral supplement is the most common type of dietary supplement used in the United States. However, many of those who take micronutrient supplements are not the target population for fortification because they already have higher nutrient intakes from their diets than nonusers.<sup>38</sup> Supplement users tend to be older, female, non-Hispanic white, physically active, and have a higher education level than nonsupplement users.<sup>37,39</sup>

It is estimated that one-third of infants, children, and adolescents in the United States consume micronutrient-containing dietary supplements.<sup>37,39</sup> Supplements clearly increase estimates of micronutrient intakes of both children and adults. The percentages of children aged 2–18 years who take supplements and have intakes less than the EAR are smaller than those of nonusers of supplements who are not meeting the EAR; this is true for vitamins D (30% versus 87%, respectively), A (2% versus 31%), and C (2% versus 21%), as well as calcium (35% versus 59%), magnesium (20% versus 37%), and phosphorus (9% versus 18%). A larger percentage of children who take supplements have intakes above the UL, as documented for zinc (52%), copper (18%), folic acid (49%), and vitamin A as retinol (45%).<sup>25</sup> It is unknown whether these high intake levels present a health risk, because most of the DRIs for children are extrapolated from adult values and are not determined experimentally, and biomarkers indicating excess are not available.

## IMPACT OF REVISED DAILY VALUES ON NUTRIENT INTAKES

DVs on a food label identify the levels of nutrients in a food expressed as percentages of a reference group's needs. The DVs for vitamins and minerals are largely based on the highest values across all age/sex groups aged  $\geq 4$  years and excluding pregnant and lactating females,

with the values originally derived from the 1968 recommended dietary allowances (RDAs). Starting in 1997, the Institute of Medicine (IOM) released a series of monographs on the DRIs for macronutrients, vitamins, and minerals. In a 2007 Advance Notice of Proposed Rulemaking announcement, the FDA proposed to use the current DRIs to update the DVs. The FDA continues to seek input on several questions, including the following: Should the DVs be based on an EAR? Should the DVs be based on an RDA? Should the DVs be population weighted or based on population coverage, using the highest value for any population group, of the EAR or RDA? Should any or all adequate intakes (AIs) be used to set the DVs?<sup>40</sup>

Revisions of the DVs on food labels currently being considered by the FDA could alter the levels of nutrients that manufacturers add to foods, which could, in turn, affect nutrient intakes. For this reason, more research on these and other issues relating to fortification is needed.

Figure 2 shows the percentage of Americans with usual intakes from food below their EAR. As part of the DRI process, an IOM Committee on the Use of Dietary Reference Intakes in Nutrition Labeling released a companion report outlining science-based principles to guide the establishment of updated reference values for nutrition labeling.<sup>41</sup> In this report, the committee recommended that the DVs for labeling be based on a population-weighted mean of EARs, or an AI in cases when no EAR exists, rather than using the population coverage RDA (using the highest RDA for adults and children aged  $\geq 4$  years, excluding pregnant and lactating women).<sup>42</sup> However, this is a controversial issue and the matter presently remains unresolved.

If the DVs are revised to levels lower than the currently used highest RDAs, and manufacturers continue to add the same amounts of nutrients in fortification, the labeled DV percentages for nutrients would increase, although this would have no effect on nutrient intakes or the nutrient status of the population if all other things were equal. However, if the revised DVs are lower than the current values and a manufacturer chooses to reduce fortification levels in order to maintain the same level of nutrient fortification based on a DV percentage, manufacturers would achieve savings on their fortification costs and intakes of the nutrient by the US population would decrease accordingly. In this scenario, a reduction in the DVs would reduce fortification levels and potentially adversely affect the nutritional status of the US population. In contrast, in cases in which revised DVs would result in values higher than current reference values, manufacturers might increase nutrients to maintain current fortification levels in order to maintain “good” and “excellent” source claims required by law on a DV percentage basis, which could conceivably increase

the percentage of the population exceeding the UL. It is presently unclear what manufacturers would likely do if the DVs were to change.

To understand the nutritional implications of the various approaches proposed for setting new DVs, the ILSI North America Committee on Fortification sponsored a fortification modeling exercise to evaluate the intake and adequacy of 15 vitamins and minerals by the US population aged  $\geq 4$  years under each of four hypothetical DV scenarios specified in the 2007 Advance Notice of Proposed Rulemaking, assuming fortification at the same DV percentages: 1) population-weighted EAR, 2) highest EAR, 3) population-weighted RDA, and 4) highest RDA (Table 2<sup>43,44</sup> and Figure 3). For each of the four hypothetical DV scenarios, total nutrient intakes and adequacy of intakes were estimated assuming that nutrients are added to or removed from each fortified food to maintain the same percentage of the current DV.<sup>45</sup> The findings from this analysis may provide critical information for the FDA and the food industry on the potential impact of various approaches under consideration for establishing updated DVs.

## DIETARY REFERENCE INTAKES

### Fortification and the upper tolerable intake levels

The UL is one of the four DRIs developed by the IOM in the late 1990s and early 2000s (Figure 4 and Table 3). It represents the first action in North America to formally recognize that, in addition to inadequate nutrient intakes, excessively large intakes may pose a risk to humans. The model for developing ULs for different nutrients is described in one of the DRI reports.<sup>46</sup>

The goal of fortification is to fortify enough foods with nutrients at levels that have previously been determined to achieve adequacy and to correct a specific nutrient deficit in the population, or to prevent a certain health condition without exceeding the UL, especially within the target population. For example, folic acid is known to play a role in decreasing the risk of NTDs, so the goal of fortification is to prevent these defects from occurring, if possible. When intakes are already adequate, there is little scientific justification for fortification. The UL for individual nutrients set by the IOM is defined as the level of usual intake that is likely to pose no risk for most individuals, and the UL is an important consideration in determining appropriate fortification levels in foods. Whether consuming fortified foods will result in total consumption above the UL for some nutrients depends, in part, on how the upper intake thresholds are estimated. It also depends on the target population.

An analysis of NHANES 2003–2006 data found that the 13% of adults aged  $\geq 19$  years who exceeded the UL for

**Table 2 Current DV versus weighted and highest RDA and EAR for select vitamins and minerals.**

Nutrient	Unit	Current DV	Highest RDA <sup>a</sup>	Population-weighted RDA <sup>a</sup>	Highest EAR <sup>a</sup>	Population-weighted EAR <sup>a</sup>
Vitamin A	µg	1,500 RE	900 RAE	754 RAE	630 RAE	531 RAE
Vitamin D	µg	10	<b>20</b>	<b>15</b>	<b>10</b>	<b>10</b>
Vitamin E		30 IU	15 mg AT	14 mg AT	12 mg AT	11 mg AT
Vitamin C	mg	60	<b>90</b>	<b>74</b>	<b>75</b>	<b>61</b>
Thiamin	mg	1.5	1.2	1.1	1.0	0.9
Riboflavin	mg	1.7	1.3	1.1	1.1	0.9
Niacin	mg	20	16	14	12	11
Vitamin B <sub>6</sub>	mg	2.0	1.7	1.3	1.4	1.1
Vitamin B <sub>12</sub>	µg	6.0	2.4	2.3	2.0	1.9
Folate	µg	400	<b>400</b>	378	330	304
Calcium	mg	1,000	<b>1,300</b>	<b>1,085</b>	<b>1,100</b>	885
Magnesium	mg	400	<b>420</b>	341	350	283
Iron	mg	18	18	11	8	6
Zinc	mg	15	11	9.1	9.4	7.7
Potassium	mg	3,500	<b>4,700<sup>b</sup></b>	<b>4,622<sup>b</sup></b>	–	–

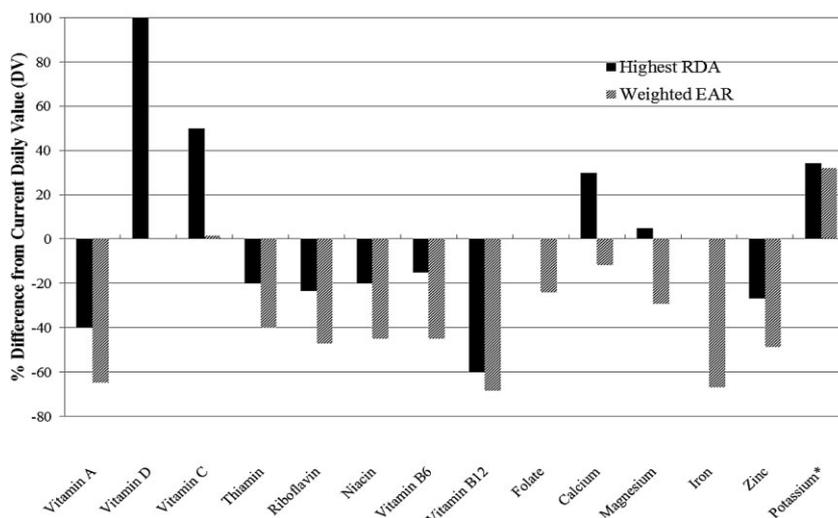
<sup>a</sup> Values in bold are greater than or equal to the current DV. With the exception of calcium and vitamin D, all values are as reported by the US Food and Drug Administration in the 2007 Advance Notice of Proposed Rulemaking.<sup>40</sup> Values for calcium and vitamin D were calculated with Population Projections Program 2005 Middle Series Census Data and 2011 DRIs.<sup>43,44</sup>

<sup>b</sup> Values for potassium are based on the AI as no EAR or RDA has been established.

Abbreviations: AI, adequate intake; AT, α-tocopherol; DV, daily value; EAR, estimated average requirement; RAE, retinol activity equivalents; RDA, recommended dietary allowance; RE, retinol equivalents.

folic acid consumed all of the following: enriched grain products, ready-to-eat cereals, and supplements containing folic acid.<sup>47</sup> However, another analysis of the entire adult population found that the percentage with total intakes above the UL was low for most nutrients

(approximately 3–8%), with niacin being the sole exception at approximately 10% above the UL.<sup>24</sup> The National Nutrition Monitoring System monitors folic acid intakes and folic acid metabolites in blood to ensure that the food supply is safe. Concerns remain that increased fortifica-



**Figure 3 Comparison of current DVs for select vitamins and minerals to highest RDA and weighted EAR.** With the exception of calcium and vitamin D, highest and population-weighted EAR and RDA values are as reported by the US Food and Drug Administration in the 2007 Advance Notice of Proposed Rulemaking.<sup>40</sup> Values for calcium and vitamin D were calculated with Population Projections Program 2005 Middle Series Census Data and 2011 DRIs.<sup>43,44</sup> Values for vitamin E are not shown due to differences in units between the current DVs and DRIs.

\*Based on the AI; no EAR/RDA was established.

Abbreviations: DRI, dietary reference intake; DV, daily value; EAR, estimated average requirement; RDA, recommended daily allowance.

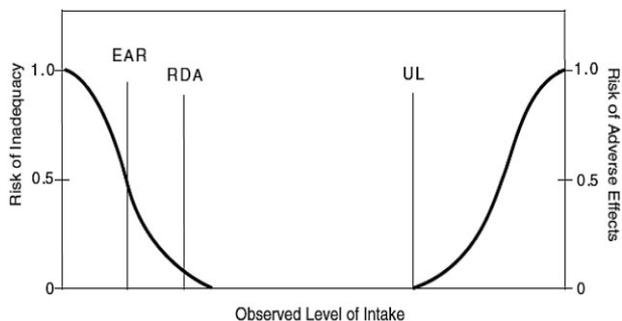


Figure 4 **Dietary reference intakes.** Adapted from the Institute of Medicine.<sup>41</sup>

**Abbreviations:** EAR, estimated average requirement; RDA, recommended daily allowance; UL, tolerable upper intake level.

tion may result in a higher proportion of intakes above the UL, which is undesirable.

It has been suggested by some researchers, however, that ULs<sup>48</sup> may be set too low, partly as a result of excessively large safety factors that account for out-of-species extrapolations (e.g., extrapolations from various experimental animals other than humans), a safety factor to extrapolate across age group and to account for between-person differences in a life-stage group, and other gross approximations including use of uncertainty factors (personal communication from Alicia Carriquiry, Iowa State University). In addition, the shape of the dose-response curve, which is unknown for most nutrients, is needed to carry out a risk assessment. Without that information, it is impossible to estimate the proportion of individuals within a group that are at risk from high nutrient intakes.<sup>49</sup> If current ULs are set too low, the proportion of persons with intakes stated to be above the UL using the current methodology is likely to overestimate the proportion of individuals at risk of harm from excess nutrient intake from all sources. As a result, the determination of excessive intakes, using the existing UL as the standard, is likely to result in conservative decisions regarding fortification. Low values for the UL can be highly protective in terms of excessive consumption, but may also have the disadvantage of resulting in an artificially low curve for nutrient intakes.

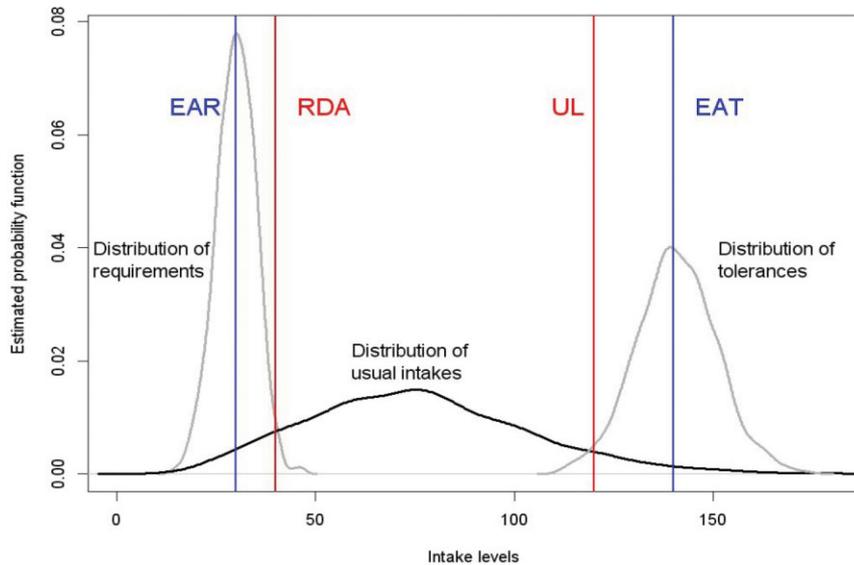
For most nutrients, the UL is likely to represent a low quantile in the distribution of the sensitivity threshold for an adverse effect, much as the RDA represents a high quantile in the distribution of requirements. It was argued in the DRI reports on assessment that using the RDA as the cut-point to estimate the prevalence of low intake in a group led to overestimating the proportion of persons with intakes below their requirements. Similarly, it is likely that using the proportion of individuals with usual intakes above the UL overestimates the proportion of individuals who may be at risk of adverse effects.

Table 3 **Definitions of dietary reference intake terms.**

Term	Definition
Estimated average requirement (EAR)	The daily intake value that is estimated to meet the requirement for that nutrient, as defined by a specific criterion of adequacy or optimal health, in half of the apparently healthy individuals in a specific life stage and gender group
Recommended dietary allowance (RDA)	An estimate of the daily average intake level that meets the nutrient requirements of nearly all (97–98%) healthy individuals in a particular life stage and gender group and assuming a normal distribution of requirements; mathematically derived from the EAR (RDA = EAR + 2 × SD)
Adequate intake (AI)	Reference intake level based on observed or experimentally determined approximations or estimates of observed median nutrient intakes by a group (or groups) of healthy people; used when there is insufficient evidence to calculate an EAR
Tolerable upper intake level (UL)	Highest average daily intake of a nutrient that is likely to pose no risk of adverse health effects for nearly all persons in the general population

However, rather than using ULs, the risk of excess may be approached in the same way as the risk of inadequacy, that is, by estimating an average tolerance for population subgroups for each nutrient and formulating a distribution of tolerances (estimated average tolerance) in the group, with a variance that reflects between-person differences.<sup>49</sup> The resulting distribution from such an approach is shown in Figure 5. The estimated average tolerance would be analogous to the EAR cut-point method at the high end that would estimate the percentage of individuals whose intakes would fall above their tolerances.

Other issues may also be important to consider in setting safety factors. The safety factors are conservative



**Figure 5 Proposed new approach for determining risk of excess nutrient intake.**

*Abbreviations:* EAR, estimated average requirement; EAT, estimated average tolerance; RDA, recommended dietary allowance; UL, upper limit.

because of the potential for nutrient-nutrient and other interactions in foods. In addition, because many different matrices occur in foods targeted for fortification, the safety factors may need to be set conservatively because the margin for differences between foods is great in terms of delivery, stability, and bioavailability. All of these issues need to be considered.

### FOOD TECHNOLOGY

All of the factors that affect the establishment and implementation of food fortification policies must be considered within the context of food technology applications and its limitations. Benefit/cost ratio calculations (benefit to public health versus cost to industry and consumers) also provide important data for policy makers as they consider whether to promote and/or implement a food fortification program. Collaboration between the food processing industry and government agencies is essential to the success of any food fortification program.

#### Food processing technologies

Technologies for adding nutrients to foods are well developed and relatively simple; however, they require significant capital investments, technically trained operators, and good analytical methods to ensure that nutrient additions are accurate, consistent, and uniformly distributed in the food. When a food is processed centrally on a large scale, it is easier to implement effective quality control procedures and to monitor the fortified food to ensure

that the amounts of added nutrients are within limits specified in government regulations.<sup>50</sup> However, as long as high quality standards and good manufacturing practices are followed, the scale of processing should not matter. Both high- and low-volume processing can create problems. Unless statistical process control is used to validate product quality and avoid process drift with the result of overaddition or underaddition, high-volume processing may cause quality issues.

Overage to ensure that label claims are met is laudable. However, overage as a strategy to cover up poor processing practices for labile vitamins should not be tolerated.

#### Food fortificants

Technologies for manufacturing vitamin and mineral fortificants are also well developed.<sup>51</sup> Synthetic forms of most vitamins that are identical to naturally occurring forms are available in high purity. In recent years, manufacturers have developed encapsulated forms to stabilize vitamins and minerals from degradation during processing and storage. Vitamin and mineral premixes formulated to the specifications of the food manufacturer are available from reputable sources at reasonable costs (see Johnson et al.<sup>52</sup> for a list of vitamin and mineral premix suppliers). However, for some nutrients like potassium, which is a shortfall nutrient, fortification may not be feasible because of alterations in the flavor profile of the food being fortified.<sup>53</sup> For other nutrients, like iron, changes in color create a barrier to consumer acceptance.<sup>52</sup>

## Benefit/cost ratios

Before a nation embarks on a fortification project, it is important to make sure that the benefits outweigh the costs. Benefit/cost ratios have been computed for several fortification regimens, and while the estimates are not precise, most appear to be greater than 1. Despite the costs of installing and maintaining equipment for adding nutrients to foods, for purchasing vitamin/mineral premixes, for validation and the added costs of quality assurance, and the costs of using comanufacturers or blenders who produce fortification premixes, the benefit/cost ratio is quite likely to be favorable but it is difficult to calculate with any degree of certainty. Benefit/cost calculations take into account the prevalence and degree of nutrient inadequacy, costs of treating nutrient deficiency diseases, assumptions on the value of a human life saved or improved, and the impact of nutrient deficiencies on worker productivity, among other factors. For example, a benefit/cost ratio for iron fortification of 6:1 has been estimated for worker productivity and 35:1 for combined worker productivity and cognitive benefits (iron deficiency can impair cognitive development in children).<sup>54</sup> In another analysis, the benefit/cost ratio for universal salt iodization was estimated to be 70:1.<sup>55</sup>

## Selection of a food vehicle for fortification

Choosing an appropriate food vehicle to carry added nutrients is key to a successful fortification program.<sup>3</sup> The food vehicle should be widely consumed by the target population, consumed on a regular basis, consumed in amounts that do not fluctuate widely from day to day, affordable to the population at risk, resistant to changes in sensory properties caused by the added nutrients, and should not adversely affect the bioavailability of the added nutrients or the stability of the added nutrients.

Food vehicles that have been employed successfully in fortification programs around the world or that show promise for fortification include wheat products (flour, bread, and pasta), maize products (corn grits, corn meal, and corn porridges), milled rice, ready-to-eat breakfast cereals, infant formulas, infant cereals, milk and other dairy products, margarines, vegetable oils, salt, sugar, soy sauce, and fish sauce.<sup>56</sup>

## Bioavailability

Bioavailability of a nutrient may be defined as the proportion of the ingested nutrient that is absorbed in the gastrointestinal tract and utilized for some metabolic function or sequestered in a storage compartment.<sup>57</sup> The bioavailability of an added nutrient can be a major factor in determining the effectiveness of a fortification

program. Bioavailability is determined by the chemical form of the nutrient, the food vehicle matrix to be fortified, the nutrient's stability within that matrix, the manner in which the food is processed and stored, the composition of the meal in which the fortified food is consumed, and the nutritional status and gut health of the consumer.<sup>57</sup> The chemical form of the nutrient, the food vehicle matrix, the processing and storage of the food, and the nutrient's stability are within the domain of food technology. The composition of the meal and the nutritional status and gut health of the consumer are in the domain of the consumer rather than the manufacturer.

Although bioavailability is important for all nutrients, it is difficult to communicate to consumers because food labeling laws quantify the total amount present per serving, rather than the amount that is bioavailable. Iron bioavailability has received the most research attention, in part because outside of heme iron sources, its bioavailability can vary from as low as 1% from oat and maize porridges in adult humans<sup>58</sup> to 22% from degermed maize powder fortified with ferrous sulfate in healthy mothers and children.<sup>59</sup> Iron is arguably the most difficult nutrient to add to foods and, therefore, was singled out to illustrate some of the challenges inherent in food fortification.

Iron fortificants are available in a variety of forms, including ferrous sulfate, ferrous fumarate, ferric orthophosphate, sodium iron ethylenediamine tetraacetic acid (NaFeEDTA), and elemental iron powders. One factor that has a large influence on iron bioavailability is the water solubility of the iron compound. In general, iron compounds that are more water soluble have higher bioavailability. Ferrous sulfate and NaFeEDTA are freely water soluble, ferrous fumarate is poorly water soluble but soluble in dilute acid, and ferric orthophosphate and elemental iron powders are water insoluble and poorly soluble in dilute acids.<sup>60</sup> Many foods contain enhancers or inhibitors of iron absorption. Ascorbic acid and meat enhance iron absorption, whereas phytates and polyphenols inhibit it.<sup>61</sup> Bioavailability from ferrous sulfate and ferrous fumarate is good unless the food being fortified contains iron absorption inhibitors, such as phytate and polyphenols.<sup>50</sup> In addition, ferrous sulfate is highly reactive and may catalyze lipid oxidation in foods, leading to objectionable odors and flavors.<sup>60</sup> Bioavailability of NaFeEDTA is lower than that of ferrous sulfate in foods that are low in iron absorption inhibitors but higher in foods that contain phytates and polyphenols, presumably because the EDTA protects the iron from binding with the inhibitors in the gastrointestinal tract.<sup>60</sup>

## Biofortification

The term "biofortification" refers to a strategy where conventional plant breeding techniques, genetic engineering,

and agronomic approaches such as micronutrient fertilizer applications are used to enhance the nutrient content and/or nutrient bioavailability of food crops.<sup>62,63</sup> Seeds from biofortified crops can be saved and planted in subsequent years so that initial investments in plant breeding and genetic engineering provide benefits extending for many years. Biofortification has the advantage of being more sustainable and less costly by eliminating the need to fortify each batch of food, as is the case with commercial fortification.

To date, the primary rationale for investing in biofortification has been to enhance the nutritional content of foods available to rural and impoverished people in developing countries who do not have access to commercially fortified foods, nutrient supplements, or varied diets.<sup>62</sup>

However, the potential for applications of biofortification in highly industrialized countries is also considerable. One example where this may be the case is biofortified rice. Rice is difficult to fortify commercially because the nutrients must be sprayed onto the surface of the rice kernel, leaving them susceptible to loss if the rice is washed prior to cooking. This would not be a problem in biofortified rice since the nutrients would be mostly on the interior of the kernel. Substantial progress has been made toward developing rice lines with enhanced concentrations of  $\beta$ -carotene, iron, zinc, folate, and essential amino acids using genetic engineering technology.<sup>64</sup> Unfortunately, none of these nutritionally enhanced rice lines has been released for farmers' use due to concerns about consumers' acceptance of genetically engineered foods.<sup>65</sup>

### "Natural" fortificants

Another approach to fortification that is gaining popularity in industrialized countries is the addition of standard micronutrient-dense products, such as dried sweet potatoes, to other foods to enhance nutrient content. This allows food companies to make "natural" label claims with "clean" labels. It is conceivable that, in the future, crops can be raised to produce fortifying ingredients that are "food derived" as opposed to "synthetic."

While biofortification strategies have tremendous potential for enhancing the nutritional quality of foods and, conceivably, could replace commercial fortification of many foods, there are several questions that must be answered before they are widely adopted in either industrialized or developing countries. These questions include the following: 1) How does biofortification of a crop affect its agronomic properties such as yield, disease resistance, water and fertilizer requirements, etc.? 2) How do environmental factors such as rainfall, soil type, etc. affect the nutrient content of biofortified crops? 3) Will consumers

and food manufacturing companies accept crops for which genetic engineering techniques were used to enhance nutrient content? 4) How is the enhanced nutrient distributed within the edible portion of the crop? 5) For example, in rice kernels biofortified with iron, is the iron primarily in the bran layer or the endosperm? If it is primarily in the bran layer, it will be lost during the milling process. 6) When seeds from biofortified crops are saved and planted in subsequent years, will the enhanced nutrient content carry through or will it revert to prior levels? 7) What is the stability and the bioavailability of the biofortified nutrient? 8) How does biofortification affect the processing properties of a food crop? For example, does biofortification of wheat affect baking quality? 9) Will it be possible to biofortify a crop with multiple nutrients at levels that are nutritionally significant? For example, refined flour and cereal products are currently enriched with iron, riboflavin, niacin, thiamin, and folic acid. If biofortification of these foods is to replace commercial fortification, all of these nutrients must be enhanced in the endosperm of the grain.

While the above questions and challenges may seem daunting, there has already been considerable progress in addressing many of them and investigators around the world are actively working on these and similar questions. A few examples of this work may be found in the literature.<sup>66-71</sup>

### The future: remaining fortification questions

Fortification has clearly improved the nutritional status of the American population for B vitamins, iodine, vitamin D, and iron. However, it is also evident that fortification is not a panacea for solving all micronutrient adequacy problems. Even with the fortification of several food products in the United States, intakes for some nutrients still fall short of recommendations, and a gap sometimes exists between nutrient intakes and nutrient status. Some of the unresolved fortification issues to be addressed in future research are outlined in Figure 6. The points that follow provide a summary of the state of fortification, what is known, and future directions: 1) There is a need to examine positive and negative implications of fortifying foods with the nutrients of concern that were identified in the 2010 US DGAs. 2) Fortification is a helpful and useful strategy for improving the nutritional status of the population, but it is not a panacea. Technical and other reasons preclude fortification with some nutrients. 3) A closer examination is needed of both the lower and higher ends of the nutrient intake curve, which are two factors used to set recommended nutrient intakes and upper tolerable levels. 4) Any change in the US DVs on food labels could have an impact on nutrient intakes – this needs to be fully explored. 5) There is a need to develop better models to

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What biomarkers for inadequacy and excessive intake are needed before fortifying the food supply with nutrients that are clearly below the EAR or AI levels?  
 Can future fortification efforts increase overall adequacy of American diets without exceeding upper levels or the limits of food technology?  
 Should some of the nutrients identified by the 2010 US DGAs as “nutrients of concern” be considered for fortification?  
 Can valid biomarkers and their optimal levels be identified for all of the shortfall nutrients and utilized as a basis for fortification?  
 Should additional fortified foods be used as representative foods for other item clusters in future updates for the USDA Food Patterns?  
 What are examples of successful fortification programs in other countries?  
 Is the broader use of biofortification of certain common staple ingredients used in food production a viable option for the future?  
 Should the current approach to determining the ULs for nutrients be re-evaluated?  
 How can the challenges regarding the effects of supplement intake on overall nutrient intakes be addressed?

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**Figure 6 Fortification issues to be addressed.**

*Abbreviations:* AI, adequate intake; DGA, Dietary Guidelines for Americans; EAR, estimated average requirement; RAE, retinol activity equivalents; RDA, recommended dietary allowance; RE, retinol equivalents; UL, tolerable upper intake level; USDA, US Department of Agriculture.

predict the impact of fortification. For example, folic acid fortification was predicted to increase consumption by 100 µg/day, but it resulted in an increase of 200 µg/day. 6) A better understanding of the repercussions of removing or reducing fortification levels is required. 7) It should be determined if children who take vitamin/mineral supplements and consume fortified foods are at risk for excessive nutrient intakes and what, if any, health consequences result or exist. 8) There is a need for a nutrient database that distinguishes fortified foods from unfortified foods. Databases for micronutrient-containing dietary supplements are also needed. 9) A liaison should be created between plant breeders and nutritionists to create the most effective biofortification with nutrients being considered for fortification.

**CONCLUSION**

This review covered several topics related to the fortification of the US food supply, focusing on an evaluation of the role that fortification has on nutrient intakes; the success of current fortification efforts; and the future role of fortification in preventing or reversing nutrient inadequacies.

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