Fortification and Health: Challenges and Opportunities[1–4]

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ABSTRACT

Fortification is the process of adding nutrients or non-nutrient bioactive components to edible products (e.g., food, food constituents, or supplements). Fortification can be used to correct or prevent widespread nutrient intake shortfalls and associated deficiencies, to balance the total nutrient profile of a diet, to restore nutrients lost in processing, or to appeal to consumers looking to supplement their diet. Food fortification could be considered as a public health strategy to enhance nutrient intakes of a population. Over the past century, fortification has been effective at reducing the risk of nutrient deficiency diseases such as beriberi, goiter, pellagra, and rickets. However, the world today is very different from when fortification emerged in the 1920s. Although early fortification programs were designed to eliminate deficiency diseases, current fortification programs are based on low dietary intakes rather than a diagnosable condition. Moving forward, we must be diligent in our approach to achieving effective and responsible fortification practices and policies, including responsible marketing of fortified products. Fortification must be applied prudently, its effects monitored diligently, and the public informed effectively about its benefits through consumer education efforts. Clear lines of authority for establishing fortification guidelines should be developed and should take into account changing population demographics, changes in the food supply, and advances in technology. This article is a summary of a symposium presented at the ASN Scientific Sessions and Annual Meeting at Experimental Biology 2014 on current issues involving fortification focusing primarily on the United States and Canada and recommendations for the development of responsible fortification practices to ensure their safety and effectiveness. *Adv Nutr* 2015;6:124–131.

Keywords: dietary intake, dietary supplements, folate, folic acid, vitamin B-9

Introduction

The International Life Sciences Institute (ILSI) North America Committee on Fortification, in cooperation with the ASN, sponsored a 2014 Experimental Biology symposium to discuss the role of fortification in meeting nutrient needs with a primary emphasis on the United States. This overview summarizes the state of current knowledge regarding dietary intakes and the possible role of fortification in the future and concludes with recommendations on responsible, safe, and effective fortification practices.

In the United States, fortification is the process of adding nutrients or non-nutrient bioactive components to food products (e.g., food, food constituents, or supplements). Fortification may be used as a tool to correct or prevent widespread nutrient inadequacies and, hence, correct associated

[1] This article is the result of presentations at the symposium "Fortification and Health: Opportunities and Challenges" held 26 April 2014 at the ASN Scientific Sessions and Annual Meeting at Experimental Biology 2014 in San Diego, CA. The symposium was sponsored by the American Society for Nutrition (ASN) and the International Life Sciences Institute (ILSI), North America.

[2] Supported by the ILSI North America Committee on Fortification. Detailed information about the group can be found at http://www.ilsi.org/NorthAmerica/Pages/Fortification.aspx. ILSI North America is a public, nonprofit foundation that provides a forum to advance understanding of scientific issues related to the nutritional quality and safety of the food supply by sponsoring research programs, educational seminars and workshops, and publications. ILSI North America receives support primarily from its industry membership, which works collaboratively with academic scientific advisors on the development of its programs. Science writer Densie Webb, PhD, RD, contributed to development of drafts of this article and received funds from the ILSI North America Committee on Fortification.

[3] Author disclosures: JT Dwyer is a public trustee of ILSI North America; serves on the scientific advisory boards of ConAgra, Inc., McCormick Spice, the Mushroom Council, the California Walnut Commission, and Bay State Milling; and is a consultant to Nestle, Inc. KL Wiemer and KB Miller are employees of General Mills, Inc. O Dary, MA Philbert, V Tarasuk, and CL Taylor, no conflicts of interest. CL Keen serves on advisory boards of AdvoCare, Herbalife, Mars, Inc., McCormick Spice, and Theralogix. JC King serves on the Scientific Advisory Board for ConAgra; has received research funding from the Almond Board of California, the California Walnut Commission, Thrasher Foundation, Harvest Plus, the Nestle Foundation, USDA, and NIH; and has provided consultation to the Alliance for Potato Research and Education and ILSI North America. PC Gaine and AB Jarvis were employees of ILSI North America when the manuscript was prepared. RL Bailey is a government liaison to the ILSI North America Committee on Fortification.

[4] The contents are the responsibility of authors and do not necessarily reflect the views of USAID or the US government.

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micronutrient deficiencies to balance the total nutrient profile of diets, to restore nutrients lost in food processing, or to make products more appealing to consumers. Nutrients may be added to foods, such as with restoration of nutritional value through enrichment of refined grains in which nutrients lost during processing (thiamin, niacin, riboflavin, and iron) are added back (1). In some cases, foods may also be fortified with nutrients not normally present, such as the addition of calcium to orange juice. Although some foods are fortified or enriched under the umbrella of FDA regulations and provisions, some foods are fortified with nutrients at the manufacturer's discretion.

The FDA established its Food Fortification Policy (2) in 1980. This policy was guided by 6 basic principles: *1*) the nutrient intake without fortification is below the desirable content for a significant portion of the population, *2*) the food being fortified is consumed in quantities that would make a significant contribution to the population's intake of the nutrient, *3*) the additional nutrient intake resulting from fortification is unlikely to create an imbalance of essential nutrients, *4*) the nutrient added is stable under proper conditions of storage and use, *5*) the nutrient is physiologically available from the food to which it is being added, and *6*) there is reasonable assurance that it will not result in potentially toxic intakes. In response to the discussions surrounding increased interest in fortification, the FDA has stated that decisions relative to food fortification should be based primarily on clinical and biochemical data rather than on dietary data alone, as had been the basis of earlier guidance on fortification (3).

Although the FDA's fortification policy remains relevant, the food environment has changed dramatically and essential nutrient deficiencies are much less common. Therefore, with the original principles in mind, it is necessary to explore how nutrient fortification contributes in the context of current nutrient intakes.

The US Experience with Fortification

Early fortification programs were developed to treat and prevent readily diagnosed nutrient deficiencies (e.g., beriberi, goiter, rickets, and pellagra) that were either epidemic or occurred in specific population groups. Today, fortification programs tend to be based on dietary intakes below recommendations on the basis of age and sex, as demonstrated by dietary surveys, rather than attempting to correct a recognized health issue or disease. Selecting a food vehicle for fortification and identifying which populations might be at risk of micronutrient inadequacies are difficult because of the diverse food patterns in the United States today.

Once the need for fortification is established, whether by prevalence of disease because of micronutrient deficiencies or low nutrient intakes, the physiologic bioavailability of fortified nutrients must be considered both to ensure safety as well as to support efficacy. Supplements taken separately from food, for example, may result in a rapid increase in plasma concentrations of the supplemented nutrient, whereas consuming a food fortified with the same nutrient may have a more gradual effect on blood concentrations because of the presence of the food matrix. This has been observed with zinc (4). For other micronutrients, such as folate, changes in serum folate could be higher in food fortification than through supplementation (5). If the focus of fortification is the health impact it will have on the population, both the total additional intake and the quality of the nutrient or nutrients supplied must be taken into account, not just the intake of the vehicle (fortified food) alone.

Fortification was initiated in the United States in 1924, when iodine was voluntarily added to salt to reduce the incidence of endemic goiter. Over the next few years, the incidence of goiter in regions of the United States, collectively known as the "goiter belt," decreased significantly. Among children in Michigan, the incidence of goiter decreased from 35% to 2.6% between 1924 and 1935 (6). Although iodine fortification of salt is now mandatory in ~120 countries worldwide, including Canada and Mexico, it remains voluntary in the United States, and the FDA does not mandate the listing of iodine content on food packaging (7). Iodine fortification of salt was followed in 1933 by the fortification of milk with vitamin D to prevent rickets based on the recommendation of the American Medical Association Council on Foods (8). Milk was chosen as the vehicle for the nutrient because it is a staple food for children as well as for pregnant and lactating women and is high in calcium and phosphorus, 2 nutrients required for normal bone development. In 1940, the Committee on Food and Nutrition (now the Food and Nutrition Board) recommended the addition of thiamin, niacin, riboflavin, and iron to flour. Bread enrichment was voluntary at that time. However, the Enrichment Act of 1942 required that all grain products crossing state lines be enriched with thiamin, riboflavin, and iron. In 1996, the Enrichment Act was modified to add folic acid to the list of nutrients that must be added to all grain products.

Attitudes about fortification and fortification policies have shifted in the United States over the past few decades. In the 1970s and 1980s, the FDA's experience with iron fortification signaled a paradigm shift in the way fortification was viewed. In 1974, the National Academy of Sciences recommended higher contents of iron fortification, based primarily on dietary intake data. The FDA then revised the standards for iron fortification on the basis of this recommendation. Iron enrichment resulted in high iron intakes among young men and concerns about iron toxicity were raised shortly thereafter. In 1977, the FDA lowered the iron content standards. The agency expressed concern about maintaining a diet of natural foods and reiterated that the focus of enrichment and fortification should be on the replacement of losses that occur during processing and the correction of established deficiencies, respectively. At the same time, manufacturers' interests shifted from addressing essential nutrient deficiencies to improving consumers' diet and health. Fortification was beginning to be recognized as a balancing act in which inadequacies were to be addressed while avoiding excessive intakes among

populations with high intakes of fortified foods. In the 1980s, the FDA fortification policy was guided by the following touchstones:

- Start with a demonstrated need
- Consider the unintended consequences
- Determine the proper fortification vehicle or vehicles and technical feasibility issues
- Study the potential impact on intakes/status for all age/sex groups
- Carry out monitoring postfortification

Although the FDA policy is not a regulation, it continues to serve "as a uniform set of principles that serve as a model for the rational addition of nutrients to foods" (2).

Although early fortification programs in the United States essentially eliminated the deficiency disease in question, a more recent fortification mandate addressed a developmental problem (neural tube defects) that was not as widespread as goiter or rickets had been. Research demonstrated that low intakes of folate in women were associated with an increased risk of neural tube defects (9). On the basis of these findings, the US Public Health Service recommended in 1992 that food be fortified with folic acid (10). The target group for folic acid fortification was women of childbearing age because the critical period for folic acid is 30 d before and 6 wk after conception. Because 50% of pregnancies are unplanned, a passive solution of fortification of commonly consumed foods was recommended (9). Cereal grains were targeted as the logical vehicle because enrichment standards were already in place. Before fortification, analyses were performed on simulated folic acid intakes ranging from 70 to 350 μg/100 g grain, including ready-to-eat cereals (3). The analyses indicated a 4-fold difference in folate intake among age groups, and the projected fortification further increased intakes among individuals with an already high intake compared with those with low intakes. It was likely that available food intake data underestimated intake, which, in turn, could lead to underestimates of projected intakes. Concerns were also raised about the risk of nerve damage among vitamin B-12–deficient persons, but cofortification with vitamin B-12 was not carried out because of inadequate data to address potential technological constraints (9). On the basis of food consumption data from NHANES (11), the folate content of foods was finalized at 140 μg/100 g enriched grain. The final amount of folate to be fortified was an accommodation of both effectiveness and safety (9).

Postfortification assessment found that between 1995 and 1999, folic acid fortification reduced the prevalence of neural tube defects by almost one-half, from 16.2 to 8.6 per 10,000 (12, 13). However, neural tube defects still occur, suggesting that insufficient folate is only one contributing factor. Although predictive modeling suggested that an additional 70–100 μg/d would be added to the diet by fortification, the actual addition was on the order of 200 μg/d based on serum folate concentrations. Between 1988 and 2006, serum concentrations of folate increased dramatically, followed by a slight decrease (14). This could be due to underreporting of food intake in dietary surveys, underestimation of the folate content in foods, the common practice of overages by manufacturers to ensure compliance, an increased use of folate-containing supplements, or a combination of these. Dietary folate data still overestimate folate inadequacy when compared with clinical measures. Based on intake, the prevalence of inadequacy is ~15–20%; based on clinical measures, inadequacy virtually disappears (15, 16).

Dietary recommendations for nutrient intakes are intended to be met over time; therefore, the usual dietary intake of a nutrient (i.e., the average of intake over the two 1-d dietary records in NHANES) is necessary to describe the prevalence of inadequate or excessive nutrient intakes (i.e., the tails of the distribution). Individuals with a high intake of a nutrient before fortification may have slightly higher intakes once fortification occurs. Dietary supplements can add substantially to the nutrient intake of individuals who use them and can alter the nature and shape of the distribution of the intake among the population. Approximately one-half of adults and one-third of children are reported to take supplements (17–20).

However, very little is known about the differences in micronutrient intakes among children, whether or not they use dietary supplements. The diets of children (aged 2–18 y) were analyzed from NHANES What We Eat in America, a nationally representative, cross-sectional survey. Fortification and enrichment were found to increase the percentage of children who met the Estimated Average Requirement (EAR)[14] for most micronutrients. Before folate fortification, at least 50% of children aged 2–8 y in the United States were not achieving the recommended intake. After fortification, however, almost 10% of children in that age group exceeded the Tolerable Upper Intake Level (UL) from foods alone; among children taking supplements, 70% exceeded the UL (21). Exceeding the UL was observed from food sources alone for several nutrients, including zinc (17%), copper, folic acid, and vitamin A (3%). The prevalence of intakes exceeding the UL greatly increased for the micronutrients when dietary supplement use was considered: zinc (52%), folic acid (49%), vitamin A (45%), and copper (18%).

The US experience with folic acid fortification and the limited data on children's nutrient intakes point to a need for caution and careful planning for future fortification programs, such as that being discussed for vitamin D. For example, better information on dose-response trajectories is needed for the nutrients under consideration. It should also be well established that those at risk are "reachable" by food fortification and that unintended consequences associated with high levels of consumption among some portions of the population, especially children, are unlikely. Better indicators of a public health need for fortification should be identified.

[14] Abbreviations used: DV, Daily Value; EAR, Estimated Average Requirement; UL, Tolerable Upper Intake Level.

Global Issues of Fortification

Elsewhere in the world, particularly in low- and middle-income countries, there are a number of fortification programs that highlight the enormous benefits of judicious fortification, as well as potential unforeseen consequences, including not reaching target populations, overconsumption of nutrients in groups outside the target population, and monitoring additional intakes and nutritional status associated with consumption of fortified foods.

Challenges described in the following examples, such as choosing appropriate fortification vehicles, reaching target populations, avoiding overconsumption in nontarget groups, and monitoring nutritional status, are relevant to all countries because they occur everywhere there is an attempt to fortify foods to optimize intakes and nutritional status. The WHO issued guidance for the fortification of maize and wheat flour in 2009 based not on the distribution of intake across different segments of the population but on national per capita intakes and assuming that no other source provided the referred micronutrients (22). However, the recommendations pointed out the following: "These estimated contents consider only wheat flour as the main fortification vehicle in a public health program. If other mass-fortification programs with other food vehicles are implemented effectively, these suggested fortification contents need to be adjusted downward as needed." This qualification has not been consistently heeded; and many times, micronutrient contents do not fit the nutritional necessities of the populations. For example, in Guatemala, vitamin A has been added to sugar since 1974 (23); and although the current serum concentrations of retinol in children and women in the poorest part of the country are the same as in the United States (24), the Guatemalan government still supplies additional vitamin A in the form of supplements every 6 mo to the children of Guatemala and micronutrient powders also include this vitamin. It is estimated that only a very few of the poorest families do not reach adequate vitamin A intake (25). Although other fortification vehicles could be considered to deliver vitamin A (26), sugar remains the most cost-efficient for Central America.

Once fortification is implemented, there is often reluctance on the part of policy makers to reduce the content of the nutrient being fortified, even in the face of evidence that higher doses are not needed to demonstrate benefit. Folic acid fortification of grain products is well established as a means to reduce the incidence of neural tube defects (27). In Chile, the consumption of wheat flour is ~200 g/d; thus, fortification with folic acid was targeted at 200 μg folate/100 g flour to deliver 400 μg folic acid. Because the fortification of wheat flour has been effective for reducing the prevalence of neural tube defects in Chile, there is little support for reducing the level of folic acid fortification despite the very high additional intake of folic acid for the overall population. There is concern that population subgroups are at risk of consuming usual intakes above the UL. A predictive analysis performed in the Dominican Republic to identify the most effective food vehicles to supply nutrients that were insufficient highlighted the importance of the WHO's statement about multiple fortification (28). Maize flour, wheat flour, and rice were considered. The results showed that 85% of the population was not eating maize flour, indicating that maize flour would not be an effective vehicle for fortification. Wheat flour consumption was found to be one-half that of the United States. Rice is a staple of the Dominican diet and is consumed by the majority of the population. Thus, the fortification of rice would have a large impact on nutrient intakes in the Dominican Republic. However, the situation is different in Mexico, where implementing a combination of wheat flour and maize flour was determined to have the best potential outcome by covering different segments of the population simultaneously while minimizing the risk of overconsumption by using lower contents of the micronutrients in both flours than by formulating each separately (29).

In Jordan, fortified wheat flour delivers sufficient iron to improve iron status in children, but the amount of iron delivered to women is thought to be inadequate. As a result of iron fortification, iron deficiency anemia decreased significantly in children from 26% to 13.7%, but no improvement was observed in women (30). In addition, the Middle East population is known for a high consumption of tea, which reduces the availability of the iron. Conversely, the vitamin A provided via wheat flour fortification in Jordan is thought to be inadequate for children but sufficient for women (31).

The use of more than one fortification vehicle for a diverse population may prove to be the most effective way to reach the largest number of people and present the lowest risk of excessive intakes (29). Several countries applied a similar strategy to determine the maximum allowable nutrient intake from fortification and to avoid exceeding the safe upper limits that have been established (32–34). It is important to approximate the magnitude of the nutritional inadequacy of the population (nutrient gap) and the combined use of food vehicles by using the average estimated intake for a specific population (29). The supply of fortified nutrients could be proportional to energy intake, taking into account both minimum and maximum values that will be fortified in the diet (fortifiable food energy) (29).

Technological Issues with Use of Nanomaterials for Fortification

Because of organoleptic issues, not all micronutrients that fall short of recommended contents (e.g., magnesium and potassium) are suitable for fortification. This presents technical opportunities that should be investigated, including the following: safety and efficacy of nanotechnology for fortification; overcoming organoleptic problems posed by some fortificants such as iron, fiber, and potassium; establishing a better understanding of bioavailability; and overcoming the degradation of certain fortificants such as vitamins B-12 and C (35). Theoretically, nanotechnology is a way to deliver nutrients in the needed amounts to the surface of specific tissues. The human body has evolved in an environment of nanomaterials (36). Formerly referred to as colloids or

colloidal suspensions, there are a variety of biologically useful nanomaterials [e.g., iron sulfur clusters in enzymes such as aconitase (37), as the by-product of low-temperature combustion of organic materials such as wood (38), and volcanic eruptions (39)]. Therefore, engineered nanomaterials do not pose a novel "size-challenge" to humans and animals but may present new morphologies and chemistries as a by-product of engineered properties that confer new physical-chemical-mechanical functions.

Nanomaterials are currently used for a wide range of applications, including the following: nanosized powders to increase the absorption of nutrients; nanoencapsulation of nutraceuticals for better absorption, improved stability, or targeted delivery; and nanochelates (coiled nanoparticles) to deliver nutrients more efficiently without affecting the color or taste of food. However, safety is a primary concern with the use of nanotechnology and must first be considered before efficacy can be addressed. Factors that make nanomaterials potentially toxic include the following:

- High aspect ratio: although able to envelope long, thin nanostructures, macrophages are unable to move them to the proximal lymphatic node to clear them from lung via the mucociliary escalator (40, 41).
- Bio-persistence: nanomaterials that move with the distribution of water or lipid can reside permanently somewhere in the body. It cannot be predicted where the permanent material will occupy biological space. The more permanent the nanomaterial, the more likely it is to have an interaction in the body—whether beneficial or adverse (41).
- Reactive surfaces: some are capable of producing reactive oxygen species, increasing potential toxicity (42–44).
- Composition and stability: nanomaterials are capable of delivering a super physiologic concentration of materials to an extremely small space, no longer benefiting from the principle of volume distribution and thus increasing potential toxicity (45, 46).

It is well understood that use of nanomaterial-containing fortificants effectively changes the pharmacokinetics of the fortificant itself. Dose metrics of the materials are complex: as the material becomes smaller, the surface area increases exponentially and therefore so does the probability that the nanomaterial will interact with something within the biological space (41). It is therefore critical to understand the potential for alterations in pharmacodynamics of nutrients, especially those that are either poorly absorbed or rapidly excreted after gastrointestinal uptake. Similarly, the particulate nature of many nanotechnologies could result in particulate accumulation in the reticuloendothelial system, resulting in malfunctioning of the innate immune system. The longer-term health consequences of engineered materials at the nanometer scale are poorly understood. A complete understanding of the consequences of subacute and chronic exposures to engineered nanomaterials will need to be acquired before they can be used widely to add fortificants to foods. The development of clear lines of authority for supervising fortification processes in industry, and regulating and monitoring their use effectively in government, must accompany advances in these technologies (47, 48).

Risks vs. Benefits of Fortification

Although there is risk in not obtaining adequate nutrients in the diet, there is also concern about whether individuals are consuming nutrients in excess. For some nutrients (e.g., zinc and copper), the window of safety between the values of EAR and UL for what represents an adequate intake vs. an excessive intake is relatively small, the difference being a factor of 4.

Currently, in Canada, discretionary fortification is occurring through Temporary Marketing Authorizations, with the nutrient additions permitted at contents well in excess of EARs for many B vitamins (49). A cursory look at the labels of novel beverages sold in a local supermarket revealed energy drinks providing as much as 6 times the EAR for vitamin B-12 and 3 times the EAR for riboflavin, for example, despite there being no evidence of inadequacy for young men (50), who appear to be the target audience for many of these products. Although single high doses of vitamin B-12 or riboflavin easily exceed human transport capacity, rendering these vitamins fairly safe, such nutrient additions are a marked departure from fortification programs designed to address demonstrated problems of nutrient insufficiency in populations.

Over the past decade, discussions around Daily Values (DVs) have centered on how they should be developed and whether changing the DVs would result in changes in the nutrient concentration in foods. However, much of discretionary fortification seems to be disconnected from the conventional view of the DVs listed on nutrient food labels and regulated language concerning nutrient content claims or diet-related claims, suggesting that discretionary fortification may be insensitive to changes in DVs. There is little evidence that usual intakes at contents in excess of nutrient requirements are of benefit. Without evidence of benefit, the question then becomes whether discretionary fortification practices can result in harm or wasteful inefficiency in the food supply. There is a need to better identify the nutritional status of individuals with respect to conditions of marginal deficiencies (e.g., for vitamin D) to fully understand the potential effects of discretionary fortification.

Despite ULs having been defined for many nutrients, the consequences of chronically high intakes from fortified foods and/or supplements is not known. Moreover, the consumption of fortified foods and supplements is correlated; people with high intakes of fortified food tend to also use supplements (51). The consumption of fortified foods results in a higher probability of nutrient intakes near or above the UL as does the intake of supplements (21, 52–55). Expanded fortification can be expected to affect the upper tails of intake distributions the most. Whether discretionary fortification is beneficial depends on which foods manufacturers fortify, which nutrients are chosen as fortificants, how much of the fortificant is added, and what portion of the population consumes the fortified products.

Individual differences can affect the outcome of fortification. Numerous gene polymorphisms can alter the digestion,

absorption, and metabolic responses of individuals to certain nutrients (56). Fortification with folic acid was initiated in part because of the identification of a high prevalence of polymorphisms in several folate-dependent genes involved with single-carbon metabolism. It is now recognized that some of these polymorphisms can significantly alter folate requirements among pregnant women (57). Another emerging area of interest that could influence the outcome of fortification is the composition of the gut microbiome. The size and diversity of the gut microbiome within specific populations can be influenced by an individual's diet, which could, in turn, affect absorption of certain nutrients (58–60).

Even less is known and understood about the potential health impact of fortification with non-nutrient bioactive food components. Flavanols can serve as an example of a non-nutrient bioactive for which research has suggested health benefits. Numerous investigators have reported inverse associations between the consumption of flavonoid-rich diets and the risk of cardiovascular disease, and there is evidence that one family of flavonoids (flavan-3-ols) is particularly of value with respect to vascular health (61–64).

Complicating the issue of potential dietary recommendations for flavanols is the fact that the bioavailability and biological activities of the 4 flavan-3-ol isomers can show considerable variability (65). This is currently an issue because the flavanol content of most foods is not provided with respect to the specific isomers that are present. A further complication is that food processing can result in changes in the flavanol stereoisomers that are present in a food or beverage. For example, heating tea at a high temperature can alter the flavanol stereoisomer profile that is present in the final product (66).

Consistent with the epidemiology, improved vascular health was reported in several intervention trials in which subjects were given flavanol-rich foods or beverages (62, 67, 68). The improvements in vascular health were attributed to a number of factors including flavanol-induced changes in the immune system, flavanol-induced reductions in platelet reactivity, and flavanol-induced improvements in vascular reactivity and vascular tissue repair. Importantly, the majority of intervention studies with flavanols were conducted in individuals with varying degrees of health complications (e.g., hypertension, diabetes, cardiovascular disease, and smoking); additional studies on the effects of flavanol supplementation in "healthy" individuals are needed before recommendations for diet flavanol fortification. Although the results of the supplementation trials have been encouraging, it must be noted that the amounts of flavanols that have been used in most trials exceed what the majority of the population currently consumes (69). This raises questions regarding what, if any, potential safety risks exist. Because higher-than-average intakes may be needed to demonstrate benefit, potential risk of some segments of the population could exist. To address this possibility, supplementation trials are needed that evaluate the safety of flavanols in amounts that exceed what has been reported to be efficacious in the clinical trials reported to date.

In addition to studies of the effects of flavanols in "healthy people," a better characterization of the flavanol status of the general population is needed. However, sensitive biomarkers to identify an individual's status with respect to the individual flavanols have yet to be identified (70, 71).

Functional biomarkers such as flow-mediated dilation, arterial stiffness, and platelet reactivity, which have been used by the European Food Safety Authority as a basis for flavanol health claims, could be considered in the future (72, 73).

Summary

Fortification is a tool that has been used successfully to correct nutrient inadequacies and their associated deficiencies. This is the classic case of mandatory fortification of staple foods. Interest in fortification has shifted from prevention of deficiencies to improving health. However, it is not known whether discretionary fortification improves health, and its long-term effects remain unknown. Fortification adds to the nutrient intakes of nearly everyone in a population.

In some countries, even basic information on existing dietary intakes is lacking. This is confounded by the nutrients for which nutrient requirements have not been clearly elucidated for given age group and sex. Accurately assessing intakes of fortification vehicles is needed to assess the dietary impact of any fortification program.

Because the need for and the effectiveness of fortification varies by age, sex, life stage, and genetic profile, groups that are at high risk of inadequacy and/or excess deserve special attention in all countries. It is evident that a greater understanding of how food intake influences biomarker concentrations is critical so that more appropriate vehicles for food fortification can be identified and better advice given to those who wish to pursue this strategy. Identifying and using biomarkers will be essential for identifying who is at risk. Furthermore, the foods to fortify as well as the micronutrient contents must be chosen carefully, to identify the most appropriate vehicles for food fortification as well as target the population at risk of inadequacy without creating excessive intakes for other subgroups of the population. Fortification must be applied thoughtfully, its effects monitored diligently, and the public informed effectively about its role in dietary intakes through labeling and other sources of consumer education. For research purposes, databases must be constantly updated to reflect the rapidly evolving marketplace, so that the contribution of both added and intrinsic micronutrients accurately estimates population intakes.

Future Directions

- There is a need to engage stakeholders to understand the importance of more comprehensive and up-to-date databases on food and nutrient intakes, and biomarkers associated with nutritional status.
- Optimal discretionary fortification requires high-quality monitoring, which will require surveys designed to enable subgroup analysis differentiating consumption behaviors

(supplements/fortificants) across all age/sex groups, especially those who are more likely to be exposed to both fortified foods and supplements.
- There is a need for better tracking/reporting systems to look for potential adverse effects of excessive nutrient exposures.
- Research is needed to elucidate the potential health consequences of chronically high nutrient intakes that are now possible from fortificants and supplements.
- Very little is known about the long-term stability of nanomaterials as fortificants, how to quantify them in food, or how they interact with the gut and the greater immune system. More research is needed.
- When discussing the issue of non-nutritive fortificants in foods, risk factors such as antinutritional effects, drug interactions, genotoxicity, and possible developmental effects must be considered. Safety thresholds must be established, the mechanisms of action better understood, and biomarkers identified before fortifying foods with these compounds.
- Because of the changes that can occur as a result of food processing, specific isomers of non-nutritive compounds must be identified and measured to make it possible to understand the link between consumption and health outcomes.

Acknowledgments

All authors read and approved the final manuscript.

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