AgBioForum, 10(3): 124-134. ©2007 AgBioForum.

Addressing Micronutrient Deficiencies: Alternative Interventions and Technologies

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Market failure for nutritional attributes of foods leads to underinvestment in crop breeding to enhance nutritional content of foods. As awareness of the importance of micronutrient deficiencies in the diets of poor people has grown, public investments in research to create biofortified staple crops have increased. The potential for this new approach is assessed in two ways. First, an examination of lessons from established interventions to address micronutrient deficiencies shows where and how biofortification can complement existing interventions and provides guidance regarding potential hurdles to successful implementation. Second, the potential for different crop-breeding technologies to biofortify crops is examined, and the advances that can only be achieved through application of modern biotechnology are identified.

Key words: market failure, biofortification, micronutrient deficiency, returns to agricultural research, biotechnology, public health.

Introduction

Improving the nutritional value of staple food crops has usually been a secondary concern for high-income consumers, who have access to improved nutrition through dietary diversification. As a consequence, the scientific improvement of staple food crops has focused on improving yield and productivity (Morris & Sands, 2006). Market forces have tended to reward higher yield far more than higher nutrient content, and crop breeders have often felt they must sacrifice the latter to get the former. This is one reason most efforts to fortify foods with micronutrients have taken place off the farm in the downstream processing and formulation of food products and often through regulatory interventions that go beyond market forces. Underinvestment in the improvement of nutritional characteristics is still the case for most private crop research in high-income countries, although work in this area is slowly expanding as consumer demand evolves. In low-income countries market incentives for biofortification research are almost entirely missing, leaving the task in the hands of the public sector.

This article examines why and how market failures persist for nutritional attributes of foods and the implications for use of modern biotechnology to address nutritional deficiencies. It also contrasts motivations in high-income countries to modify crops for nutritional enhancement with those in developing countries. The article compares the role of biofortification to other potential interventions, such as industrial fortification of conventional foods at the processing stage. Next, it shows the limitations of current approaches and point to the target populations that perhaps only a biofortification strategy can reach. Finally, the article examines the different methods available to crop scientists for introducing improved nutrient properties into crops, and identify what can only be achieved through use of more advanced techniques.

Failures in the Market for Nutritional Quality

There are failures in both the demand for and the supply of nutritional quality. On the demand side, consumers rarely have full information about either the short- or long-term effects of dietary choices. Constraints of income, cultural practices, tastes, and habits are much stronger determinants of food choice than nutritional quality. Moreover, even if one food out-performs a similar food in terms of nutrient content, that is often not verifiable to consumers. Furthermore, many nutritional deficiencies have subtle effects that appear over time and are difficult to associate with specific food choices. For example, Vitamin A deficiency (VAD) is associated with reduced immune system functioning and a higher incidence of illness and complications from illness. But this effect is not apparent to the individual consumer or household. Similarly, widely consumed trans fatty acids in partially hydrogenated oils have been found to significantly increase coronary heart disease in the US population (Mozaffarian, Katan, Ascherio, Stampfer, & Willett, 2006), but such effects were not apparent to individual consumers. Without verifiable, specific infor-

Table 1. Micronutrient deficiencies and their estimated impacts.

Micronutrient	Estimated impact and efforts to address
Iodine	Associated with brain damage. Easily mitigated with iodized salt. While incidence has declined dramatically in recent years due to the universal adoption of salt iodization starting in 1993, WHO estimates that 54 countries still have some iodine deficiency.
Vitamin A	Associated with blindness and increased risk of disease and death for small children and pregnant women. Can be addressed through supplements, which are now estimated to reach children at least once a year in 40 countries. The UN Standing Committee on Nutrition (UN/SCN) estimates that 140 million children and 7 million pregnant women are VA deficient, primarily in Africa and South/Southeast Asia. In 1998, WHO, UNICEF, Canadian International Development Agency, USAID, and the Micronutrient Initiative launched the VA Global Initiative. This provides support to countries in delivering VA supplements.
Iron	Associated with maternal death, impaired physical and cognitive development, increased risk of morbidity in children, and reduced work productivity in adults. Can be addressed through fortification of wheat products. WHO estimates 2 billion people are anemic, and this is frequently exacerbated by infectious diseases. Malaria, HIV/AIDS, hookworm infestation, schistosomiasis, and tuberculosis contribute to a high prevalence of anemia in some areas. Efforts to increase iron intake must be accompanied by efforts to control infectious disease.
Zinc	Associated with reduced immune status in neonates and children. Preliminary research shows that additional zinc can reduce incidence of diarrhea and pneumonia in children and improves maternal health. One estimate shows zinc as close to iron deficiency in contribution to the global burden of disease. Can be provided through supplements.
Folate	Deficiency associated with increased risk of maternal death and complications in birth; also associated with neural tube defects in infants and with an estimated 200,000 severe birth defects every year. Can be addressed through fortification of wheat products.

Note. Data from Shekar, Heaver, and Lee (2006); UNICEF/MI (2004); UN/SCN (2004); and World Health Organization (2004).

mation associated with a particular food product, consumers will not choose one food over another on the basis of nutritional quality.

On the supply side, producers may also have incomplete information about the foods they produce, particularly foods that are not standardized. With few incentives in the market, investments in nutritional enhancement of foods or even in provision of nutritional information will be not be made by the private sector. Thus, nutritional deficiencies in diets have been addressed through a variety of policy measures, including mandated changes in processed food composition, mandated disclosure of product content information, providing consumers with supplements and supplemented food through targeted outreach, and provision of nutrition information and education. Biofortification represents a relatively new approach, and the few examples of its implementation are discussed in the article "Patterns of Political Response to Biofortified Varieties of Crops Produced with Different Breeding Techniques and Agronomic Traits," elsewhere in this special issue.

The nature of the market failure in nutrition changes as economies develop and diets change. Micronutrient deficiencies, often compounded by calorie and protein deficits, are important sources of lost health and life (as measured by disability-adjusted life-years, or DALYs) in poor economies. Even with information about potential health benefits, resource-poor households may not have the ability to meet the needs of those most at risk, such as small children and pregnant or lactating women. Diets improve with income, but this is a lagging effect, particularly for some micronutrients. The lag can be shortened through improvements in women's education and access to safe water (Smith & Haddad, 2000) but can still persist due to the structure of food preferences.

With higher incomes, chronic diseases resulting from consumption of fats and sugars become more important health risks. It appears that this transition is occurring more rapidly in countries now in the middle income range (Popkin, 2001), and thus, both established policies and new types of intervention may be needed to address this "dual burden" of over- and under-nutrition in developing countries. Next, the article considers the extent of micronutrient deficiencies and the limitations of existing interventions.

Micronutrient Deficiencies and Potential Interventions

The importance of micronutrient deficiencies is well known and documented (see Table 1). According to the World Health Organization (WHO),

> "more than 2 billion people in the world today are estimated to be deficient in key vitamins and minerals, particularly Vitamin A, iodine, iron, and zinc. Most of these people live in low-

> income countries and are typically deficient in more than one micronutrient" (WHO, World Food Programme, & UNICEF, 2007).

Deficiencies of iodine, Vitamin A (VA), and iron are the most important for global public health in terms of numbers of individuals in a position to secure large benefits; folate and zinc have important but more limited or less understood impacts. The World Bank estimates that $180 billion in lost productivity globally could be prevented with only $4 to $5 billion invested in deficiency prevention, using currently available technologies (Behrman, Alderman, & Hoddinott, 2004). It is now recognized that micronutrient deficiencies are persistent public health problems that require direct intervention during the process of economic development.

The widespread recognition of the importance of micronutrient deficiencies to global health, and the potential to address such deficiencies relatively cheaply through fortification or supplementation, has led to several multilateral efforts to support traditional interventions. These various established alternatives to biofortification are examined for their potential and their limitations, with particular attention to industrial fortification as the intervention with the widest scope and most overlap with biofortification efforts.

Supplementation

Periodic provision of supplements (often in the form of tablets) can address deficiencies of micronutrients that are stored in the body, such as VA and iron. Supplementation can be cheap compared to the large public health benefit. The total annual cost of iron tablet supplementation in India to reach 27 million women and 128 million children at risk is only $5.2 million. Yet even small budgets can be difficult to sustain year after year when they are dedicated to the welfare of politically weak or socially marginal beneficiaries. Furthermore, while certain populations are easy to reach through existing institutions (e.g., schoolchildren through schools), it is often difficult to accomplish full coverage of those most at risk—poor women and very young children. Thus, supplementation has often been most effective when delivered together with other maternal and child health interventions.

Promotion of Dietary Diversification

Education is an important element in ensuring that improvements in income result in better maternal and child health. However, dietary diversification is constrained by resource availability for poor households and seasonal availability of fruits and vegetables. Promotion of home gardens is often touted, but the poor have a high opportunity cost for their labor and often limited land. Increased production of fruits and vegetables for household use reduces resources available for other income-earning or food-production activities. This type of effort is also relatively expensive and difficult to sustain on any large scale.

Industrial Fortification

The marketed supply of a widely consumed staple food can be fortified by adding micronutrients at the processing stage, and historically this is how micronutrient deficiencies have been addressed in the developed world. Food fortification has a long history, having been promoted, accepted, and implemented in North America since the 1920s. Effective implementation requires private sector cooperation (Bishai & Nilubola, 2002), and the food industry in the United States has seen fortification as a public service and a way of building demand, which made compliance with mandated programs easier to achieve over time. Concentration in the food industry also tends to strengthen compliance and quality assurance. The efficacy of fortification in addressing historical dietary deficiencies is unquestioned in *developed* countries, providing some consensus for its appropriate use in *developing* countries (Food and Agricultural Organization [FAO], 1995).

Interest in traditional industrial fortification of foods in developing countries has increased in recent years as NGOs have enlisted cooperation and support from the private sector. Such efforts are timely in light of the growing consumption of processed and packaged foods (Regmi & Gelhar, 2005). Consumption of wheat flour products is growing around the world, even where wheat it is not a traditional food staple, opening new fortification opportunities at the milling stage. Political support for traditional fortification has recently been enhanced by three new promotion and coordination efforts: Micronutrient Initiative (based in Canada), Flour Fortification Initiative (based in Emory University), and the Global Alliance for Improved Nutrition (GAIN, based in Geneva). Other important global actors include the Network for Sustained Elimination of Iodine Deficiency and the International Zinc Nutrition Consultative Group. In addition, efforts are underway to set regional standards for fortification. These were successfully concluded in Central America in the late 1990s (Bishai & Nilubola, 2002) and are currently underway for Southeast Asia under the leadership of the International Life Sciences Institute (ILSI).

In 2005 in Beijing, GAIN, together with the World Bank Institute (WBI), brought together 150 business leaders from all along the global food supply chain to form a Business Alliance for Food Fortification (BAFF). This forum produced a "Beijing Declaration on Food Fortification," which expressed confidence in fortification as a proven means to reduce vitamin and mineral deficiencies and to improve nutrition levels among poor populations. Coca-Cola, Danone, and Unilever agreed to become the first co-chairs of BAFF, which requires annual reporting from member companies on progress toward increasing vitamin and mineral coverage of poor populations.

The Flour Fortification Initiative provides an assessment of global progress through September 2007 and they report that 26% of the global wheat market is fortified, benefiting 1.8 billion people. Most wheat fortification efforts in the developing world are still preliminary or on a pilot scale; they are primarily in the Western Hemisphere, with little sustained activity in Asia and Africa, where most of the micronutrient deficient populations live. The Shekar et al. (2006) report that consumption of iodized salt is not widespread in either South Asia or Sub-Saharan Africa, even though this type of fortification is cheaper and easier to achieve. Thus, in spite of greater attention to fortification, its coverage remains low in the regions where micronutrient deficiencies are most important.

Food fortification programs in developing countries continue to face significant structural hurdles (Bishai & Nilubola, 2002). These include the less concentrated structure of the food industry, making private cooperation more difficult to achieve; price and market controls still in place for many food staples that reduce profitability and hence, industry motivation; and the lack of consumer awareness or effective demand for nutrients, which is necessary in the long run to sustain industry motivation. These programs are still limited in their capacity to reach the very poor, particularly those consuming rice- or maize-based diets. Certain kinds of fortification may be impractical for some important food staples (e.g., VA fortification of milled rice), or may introduce off-colors or flavors (e.g., VA fortification of white maize).

While industrial fortification efforts are becoming more widespread in developing countries, such efforts are limited by their continuing costs and by the imperfect coverage of the target population, particularly the rural poor and young children. Where mandatory, fortification costs are most often borne by food processors, such as flour millers, and they may resist this imposition. Such mandates also may be impossible to enforce where food processing is carried out by many small and widely dispersed firms. Industrial fortification will only apply to marketed supplies and therefore may not reach those among the poor who obtain food outside of commercialized channels. Given these limitations, it is clear that industrial fortification of food cannot provide a complete solution to the problem of micronutrient deficiencies in the medium term. It is in this context that a role emerges for biofortification as a complementary strategy.

Lessons for Biofortification

There are several lessons from these established interventions for the design of biofortification efforts, especially regarding costs, feasibility, acceptance, and safety. The established interventions have all been limited in scope, due to the recurrent budget costs and limited coverage in rural areas. The relatively lower cost associated with building nutrients directly into the seeds of crops makes biofortification a potentially cost-effective and sustainable intervention. This is an important motivation for biofortification.

Several studies have documented the relative cost-effectiveness of biofortification. For example, Stein (2006) estimates for India that saving one DALY through VA *fortification* costs US$84-98; through VA *supplementation* it costs US$134-599; and through biofortified Golden Rice (genetically engineered to contain VA precursor) it will cost between US$3.40-35, substantially less than either of the other interventions. Dawe, Robertson, and Unnevehr (2002) compared Golden Rice with wheat fortification in developing Asia, and found that cost per retinol activity equivalent (RAE) delivered was comparable for Golden Rice with low beta-carotene levels. Its cost-effectiveness would be substantially greater with the higher levels of beta carotene achieved in subsequent research (see the case study on Golden Rice elsewhere in this special issue, Dawe & Unnevehr, 2007). These results reflect the fact that it is fundamentally cheaper to build nutrients into the crop than it is to incur the costs of fortification indefinitely into the future.

Qaim, Stein, and Meenakshi (2007) provide a review of ex-ante evaluations for biofortification in several countries. The cost per DALY saved varies from $799 for beans in Brazil to $2 for rice in Bangladesh. Among 15 different applications of biofortification considered in developing countries, the cost per DALY saved was almost always less than $100 and most often less than $50. If cost-effective health interventions are those that cost less than $200 to save one DALY, as identified by the World Bank, then biofortification promises to be a rewarding public health strategy (Qaim et al., 2007).

The wide range of cost estimates reflect uncertainties about how biofortification will work in practice. Cost per DALY saved go down as the feasible amount of nutrients in the crop rises; as the retention of nutrients in processing and marketing is maintained; as the uptake of the biofortified crops increases; and as research, development, and delivery costs decrease. As considerable uncertainty remains about these parameters, specific crop applications must still be evaluated for their feasibility and cost-effectiveness in particular populations. However, it is clear that any opportunity to jump over the long lag between income gains and dietary diversification will have significant public health benefits.

Another lesson from past interventions is that biofortification, like mandatory industrial fortification, must first do no harm in terms of posing any new or additional risks to consumers or any significant subpopulation of consumers. Safety issues are a special concern when modifying a traditional food staple that accounts for a large share of caloric intake, particularly for small children. Thus, biofortified crops will need to meet a high safety standard. Traditional industrial food fortification requires risk assessment in setting the level of the fortificant plus quality assurance in processing to ensure consistent levels are delivered in the final product (FAO, 1995). The appropriate levels of certain fortificants, such as iodine in salt, are well-established, due to a long history of food fortification beginning in the United States in the 1920s.

More recent regulations pay special attention to subpopulation nutrition risks, as understanding of those risks has advanced. For example, the 1996 folate fortification regulation risk assessment in the United States considered whether additional consumption among the elderly would mask the hematological signs of pernicious anemia (Drug Therapy and Hazardous Substances Committee, Canadian Paediatric Society, 2004). In a developing-country context, one potential risk is the interactions among some nutrients, such as Vitamin C and iron. While Vitamin C can facilitate uptake of iron, the body's stores of Vitamin C are reduced by increased iron intake (FAO, 1995). Because of these kinds of potential risks, any fortification standard must be reviewed for its impact in the particular diets of targeted populations and for any unintended risks in specific subpopulations.

Biofortified crops presumably will need to meet an equal safety standard to conventional fortification in terms of providing nutrients that are effective in alleviating deficiencies but not harmful to any subpopulation. Yet unlike industrial fortification, variations in the nutrient content of a biofortified crop could be more difficult to control, since they will depend on the agricultural practices of farmers in differing production environments. Information on the impact of different cultivation methods, weather, and preparations could thus become essential to making comparable safety determinations for biofortified crops.

If biofortified crops are produced using genetic engineering, they will have to measure up to an even higher standard, since this is a technology most countries have decided to regulate using a "precautionary principle" so that scientific uncertainty about an unknown or immeasurable risk can be enough to disqualify a technology from approval for use. The GMO (genetically modified organism) crop varieties approved so far have shown themselves to be no more risky to human health or the environment than the conventional varieties of these same crops, a view officially endorsed by the academies of science and medical councils in the United Kingdom (British Medical Association, 2004), Germany (Helt, 2004) and France (French Academy of Medicine, 2002; French Academy of Sciences, 2002). A US National Academy of Sciences (NAS, 2004) report on approaches to assessing health effects of genetically engineered (GE) foods outlined the potential for any genetic manipulation to introduce unintended effects. This report identified the method most likely to produce unintended effects as mutation breeding, yet this is a method that has been used for decades with no ill effect and little controversy in Europe, the United States, and elsewhere. Even conventionally bred crops can produce negative unintended effects, such as high levels of natural toxins. Nonetheless, so long as a social perception remains that genetic engineering is inherently more dangerous, the regulatory systems it must confront will be stricter.

How Can Biotechnology Address Nutritional Needs?

Next, we review what technologies are available and how are they currently being applied to nutritional enhancement. A review of the biofortified crops that have either been introduced or are under development is found in "Patterns of Political Response to Biofortified Varieties of Crops Produced with Different Breeding Techniques and Agronomic Traits" later in this special issue. This section reviews what the application of modern biotechnology can bring to biofortification and nutritional enhancement.

Conventional Plant Breeding

This allows crop scientists to make significant improvement in the nutritional, eating quality, and agronomic traits of major subsistence food crops. Conventional breeding is limited, however, because it can only use the genetic variability already available and observable in the crop being improved, or occasionally in the wild varieties that can cross with the crop. Furthermore, conventional breeders usually have to trade away yield and sometimes grain quality to obtain higher levels of nutrition. One example is quality protein maize (QPM), which has taken decades of conventional plant breeding work to develop into varieties acceptable to farmers. However, multiple gains are at times possible, as with iron and zinc in rice and wheat, where the characteristics that lead to more iron and zinc in the plant can also lead, by some accounts, to higher yield. Other biofortified crops, such as the orange-fleshed sweet potatoes (OFSP) promoted through the HarvestPlus program in Africa, have been successfully selected and developed for both nutrient and (at least rainy season) yield traits.

Tissue Cultures

Modern tissue culture techniques can allow scientists to reproduce plants from a single cell. These techniques are now used extensively to produce disease-free planting material of clonally propagated crops such as bananas. When tissue culture is combined with embryo rescue techniques, plant breeders can use the genes from wild and weedy relatives of a crop, which would normally not cross with the cultivated crop. This allows breeders to increase genetic variability of the cultivated crop and then bring in valuable traits of the wild and weedy relatives. These techniques have allowed scientists to cross Asian and African rice varieties and develop Nerica rice varieties with agronomic traits, such as higher yield and resistance to water stresses, that have met with growing success in Africa. Tissue culture is an important tool for propagation of roots and tubers, such as potatoes and cassava, and both of these crops are part of current biofortification research.

Mutation Breeding

Mutation breeding has been used extensively in developed and developing countries to develop grain varieties with improved grain quality and in some cases higher yield and other traits. This technique makes use of the greater genetic variability that can be created by inducing mutations with chemical treatments or irradiation. The FAO/International Atomic Energy Agency (IAEA) website contains more than 2,500 varieties that have been developed through mutation breeding (Mutant varieties database). Of these, 1,568 are in Asia, 695 in Europe, and 165 in the United States. Most of the European and US mutants are flowers, but most in Asia are basic food crops such as wheat, rice, maize, and soybeans. According to their website, FAO/IAEA include biofortification as one of the objectives of their mutagenesis program, but there do not seem to be any applicable results yet. Varieties produced using mutagenesis can be grown and certified as organic crops in the United States, whereas transgenic crops developed using recombinant DNA (rDNA) technology cannot.

Molecular Breeding

Also called marker-assisted breeding, this is a powerful tool of modern biotechnology that encounters little cultural or regulatory resistance and has been embraced so far even by organic growers because it relies on biological breeding processes rather than engineered gene insertions to change the DNA of plants. This technique is expanding rapidly with the development of genomics, which is the study of the location and function of genes, and with the rapid decline in costs of screening plant tissue. Once scientists have identified the location of a gene for a desirable trait, they build a probe that attaches itself only to a DNA fragment, a so-called marker, unique to that gene. They then can use this marker as a way to monitor and speed up their efforts to move this trait into relatives of the plant using conventional breeding. For example, since the marker can be detected in the tissue of new seedlings, the presence or absence of the desired trait can be determined without having to wait for a plant to mature, often reducing by years the length of a typical crop-development process. If molecular breeding reduces the number of generations required to develop a pureline variety by three generations, this can save three years of research time.

Use of molecular breeding has increased dramatically both by private seed companies and government plant breeders in developed countries, and it is gradually spreading to developing countries (Pray, 2006). Using this technique, plant breeders also can stack into one variety several different genes that code for different traits. For example, Asian government scientists have been working with the International Maize and Wheat Improvement Center (CIMMYT) to stack into maize a number of traits such as QPM, disease resistance, and drought tolerance (Pray, 2006). This technique has also been used to find recessive traits in plants that cannot be located by conventional breeding or other techniques.

Genetic Engineering

Genetic engineering, or rDNA, is a technique that offers still greater speed and reach because it moves specific genes with desired traits from a source organism—one which does not have to be a related organism—directly into the living DNA of a target organism. The *transgenic* trait is added without normal biological reproduction, but once in the plant it becomes inheritable through normal reproduction. Scientists first developed this technique in the laboratory in 1973 and have been using it to transform agricultural crop plants since the 1980s. Once a useful gene has been identified (which can require a major research project and many years), it is attached to both marker and promoter genes and then inserted into a plant, usually using a non-viable virus called Agrobacterium as a carrier. GE produces plants that are known as transgenics, or less precisely as GMOs.

GE has great reach because it can add valuable characteristics that are not currently found in the seeds of individual plant species. GE was necessary for the development of Golden Rice, which contains the precursor to VA from a daffodil plant. This was a trait missing from rice plants, and it could not be introduced conventionally since daffodils cannot be crossed with rice plants. In addition, GE can take much less time to incorporate desired traits into a crop plant than either traditional or molecular breeding.

The choice of which technology to use when biofortifying crops comes down to a calculation by breeders of how to get the best results most quickly, given their budget constraint. Conventional plant breeding requires less investment in labs or highly trained human resources (molecular biologists) than either marker-assisted selection or genetic engineering, and it faces lower and less costly regulatory hurdles. However, if there are no genes for the VA precursors in the genome of a crop (as one example) no amount of conventional plant breeding can put them there, and scientists must turn to GE. Molecular breeding and GE also have advantages over traditional breeding because they make it easier to

- *develop crops with multiple desired nutritional traits*. For example, high-lysine corn already exists, but marker-assisted selection and molecular breeding will make it feasible in the next 4-5 years to develop corn with more of three other essential amino acids, such as tryptophane.
- *maintain agronomic viability of biofortified crops.* Transgenics can make it feasible to address agronomic deficiencies that arise when nutritional characteristics are altered. Low-phytate crops, which are more digestible, have agronomic deficiencies. In order to shut off phytate formation only in the seed (not the rest of the plant), transgenic techniques are required.
- *adapt agriculture improvements arising in the United States for obscure crops in developing countries.* For example, the techniques developed for soy digestibility and protein improvement can be applied to other legumes that are important in least developed countries (LDCs), such as the *Lathyrus* spp., an important legume in India and an "orphan crop." This application will require transgenics.

Given the many tools now available for altering crop characteristics, what specific investments are being made in nutritional enhancement? Above, we argued that market failures lead to underinvestment in nutritional improvement. Two databases support our contention that relatively little crop research effort has been devoted to nutritional enhancement. A search of the USDA's database of GE crop plants that have completed US government review shows only 4 entries for nutrient-enhanced traits (out of 124). These include altered oil profiles for soy and canola and high-lysine corn. FAO's database of crop biotechnology products in use or development in developing countries also shows very few applications for nutritional enhancement (FAOBioDec). Out of more than 2,000 entries, only 125 relate to quality enhancement (which includes mostly delayed ripening or extended shelf life of fruits), and far fewer of those address nutrition. Most nutritional applications reflect transfer of US technology in maize (protein enhancement) or oilseeds (oil profile enhancement); only seven entries relate to vitamin enhancement of crops, and most of these referred to work on Golden Rice in the Philippines and Vietnam.

Table 2 provides a summary of nutritional enhancements in crops that are either currently available or

Table 2. Examples of enhanced nutritional characteristics in crops.

	Low-income consumers	High-income consumers
Nutrient characteristics	• **Improve amino acid profile for more complete protein in maize, sorghum, soy** • **More protein in potato, cassava** • Address micronutrient deficiencies: • Vitamin E in oils • Caretonoids in mustard, canola oils • Folic acid in rice, maize • Iron and zinc in rice, sorghum, maize, beans • **Beta-carotene in rice, sorghum**, maize, **cassava**, yam, sweet potato, **potato** • Iron in wheat	• Improve oil profile in soy, canola, corn, sunflower, to reduce risk of coronary heart disease, e.g., low-linoleic soy and canola, lower saturated fat content in maize oil, high oleic in soy • **Long chain Omega 3 fatty acids in soy or corn oils** • Phytonutrient content increased, such as suphrophane in broccoli, lycopene in tomatoes, isoflavones in soy • Vitamin E in lettuce (Japan) • **Alter glycemic index in corn, wheat, rice to prevent diabetes** • **Produce inulin (a prebiotic) in crops where it does not occur naturally** • Leverage benefits of soy protein for cholesterol reduction
Bioavailability	• **Lower phytate in corn to improve iron and zinc uptake** • Lower toxicity in potatoes, cassava • Improve digestibility in beans, **sorghum**	**Improve digestibility for animal feeds such as maize, soy**, to improve meat production efficiency, reduce animal waste externalities, and improve meat quality, e.g., increase phosphorous uptake from maize in animals to reduce its excretion

Bold = *Improvements that require genetic modification techniques not considered "conventional," such as transgenics or altering the action of genes.*

Note. These improvements either exist or can be realized within the next 10 years. Data from African Biofortified Sorghum Consortium (ABSC) website; Donald Danforth Plant Science Center website; HarvestPlus (2004); ISAAA (2007); H. Glick, personal communication (July 28, 2006); G. Kishore, personal communication (July 28, 2006); D. Stark, personal communication (February 22, 2007); and Pew Initiative on Food and Biotechnology (2001).

might be available within the next decade, divided as to whether the principal benefit will go to high-income or low-income consumers. The areas of overlap between research for high-income and low-income consumers are few due to the differing nutritional status and health needs of these groups. This factor reduces potential spillover benefits from commercial research in industrialized countries.

In high-income countries, the most prominent diet and health issues relate to obesity, allergenicity, and chronic diseases such as cancer or coronary heart disease, providing science with an incentive to alter oils or to improve phytonutrient content. Because there is little consumer demand for improved digestibility or protein content, and because most grains are consumed as animal feed, much of the scientific research that does take place to improve nutrition in crops is focused on their use in animal feeds.

Crop research to address human nutrition is relatively recent, as the typical consumer has only in the last two decades become more aware and more demanding regarding health attributes of foods. Information is important in leading demand, and the health-labeling policy for foods can be a major force shaping demand for better nutrient composition in foods. For example, the January 2006 US requirement to add trans fat content to mandatory nutrition labels on packaged foods has spurred investments in canola and soybean oils to generate varieties with enhanced oil profiles that can substitute for partially hydrogenated oils (which have trans fats). In anticipation, Monsanto introduced a low-linoleic soybean variety in 2005. This oil characteristic provides soybean oil with greater stability and shelf-life. It has been adopted by food processing and food service firms as a substitute for partially hydrogenated soybean oils, and production has expanded rapidly over only two years to 1.5 million acres producing 1 billion pounds of oil (D. Stark, personal communication, February 22, 2007). Soybean varieties with this characteristic had been identified in the 1980s, but little private research investment was made until regulatory action created a market for substitute oils.

In rich countries it is relatively simple to develop, target, and deliver new crops with nutritional characteristics because purchasing power is high and infrastructures and market mechanisms exist to segregate and deliver specific crop characteristics to the food processing or feed markets. However, issues of agronomic viability and market volume still constrain such developments, even when demand for consumer traits is clearly apparent. For example, the low-linoleic characteristic in soy would be less attractive in the market were it not available in the glyphosate-resistant GMO soybeans most US farmers now prefer to plant for production-cost reasons, and its use in foods remains constrained in the short run by the need to develop dedicated supply chains. Market coordination often constrains nutritional enhancements in the US food supply, and it typically takes time for such innovations to become widely adopted.

The nutritional needs of low-income consumers are different and, as discussed above, far less likely to be met through private markets. The very poor suffer from too few calories as well as from low quality calories with too little protein or micronutrients. A number of potential enhancements would address such deficiencies (Table 2), including enhanced micronutrient content of traditional staples, improved protein quality, and digestibility. Altering the staples, such as sorghum and cassava, that are most important to poor people who are difficult to reach through other means will require more advanced tools of modern biotechnology. These tools are being employed to enhance both the nutrient content and agronomic viability of these "orphan crops" (ABSC website, Donald Danforth Plant Science Center website).

Research for biofortification and enhanced nutrient content has been left to the under-funded public sector, and often even orphaned there, falling far behind agronomic characteristics in importance within national agricultural research systems. Most of the efforts summarized in Table 2 are taking place under the HarvestPlus initiative of the CGIAR (Consultative Group on International Agricultural Research), primarily with funding from the Bill and Melinda Gates Foundation. Thus, biofortification efforts are not yet widely embraced in national agricultural research systems.

Conclusions

There is underinvestment in nutritional enhancement of foods due to lack of information and market incentives and the potential conflict with agronomic improvement. Historically, nutritional deficiencies have been addressed through a variety of interventions beyond the farm gate. While efforts to advance industrial fortification of foods have accelerated in developing countries during the past decade, such efforts cannot reach all of the populations most at risk from micronutrient deficiencies. The advent of modern biotechnology, together with widespread appreciation of the importance of nutrition, has opened the door for crop modification to address nutrition. The last decade has seen increased investments in crops with improved nutritional traits, although this is still a small part of the total agricultural research portfolio in both wealthy and poor countries. In wealthy countries, the focus has been on traits that might reduce the risk of heart disease or cancer. In poor countries, the private sector faces fewer incentives to invest and the public sector focus—often funded by international donors—has been on protein, VA, iron, and zinc. Biofortification with these micronutrients has the potential to be a highly cost-effective public health intervention, particularly if it can reach populations that other interventions have missed.

Scientists are using both GE and a range of non-GM methods to produce biofortified or nutritionally enhanced food crop varieties. Some of the most challenging applications with greatest potential benefit to the poor who are outside of traditional market channels, e.g., in sorghum and cassava, will require the use of genetic modification. Furthermore, biofortified crops with acceptable agronomic traits are likely to be developed in a timely manner only through the use of molecular breeding. Thus, the tools of modern biotechnology hold great promise for alleviating nutritionally deficient diets earlier in the development process than would otherwise occur. It remains to be seen how the social and political acceptance of modern biotechnology will shape the role that it plays in meeting this important global public health goal.

References

African biofortified sorghum consortium (ABSC) project overview website. Retrieved October 22, 2006, from http://supersorghum.org/project.htm.

Behrman, J., Alderman, H., & Hoddinott, J. (2004, February). *Hunger and malnutrition* (Copenhagen Consensus Challenge Paper). Copenhagen, Denmark: Author.

Bishai, D., & Nilubola, R. (2002). The history of food fortification in the United States: Its relevance for current fortification efforts in developing countries. *Economic Development and Cultural Change*, *51*(1), 37-53.

British Medical Association. (2004, March). *Genetically modified foods and health: A second interim statement*. London, England: Author.

Dawe, D., Robertson, R., & Unnevehr, L. (2002). Golden Rice: What role could it play in alleviation of Vitamin A deficiency? *Food Policy*, *27*, 541-560.

Dawe, D., & Unnevehr, L. (2007). Crop case study: GMO Golden Rice in Asia with enhanced Vitamin A benefits for consumers. *AgBioForum*, *10*(3), 154-160. Available on the World Wide Web: http://www.agbioforum.org.

Donald Danforth Plant Science Center, International Programs, Cassava Projects. Retrieved October 22, 2006, from http://www.danforthcenter.org/international/2_Cassava%20Projects.htm.

Drug Therapy and Hazardous Substances Committee, Canadian Paediatric Society. (2004, January). *Periconceptional use of folic acid for reduction of the risk of neural tube defects* (Position Statement Reference No. DT95-01). Ottawa, Ontario, Canada: Author. Retrieved October 15, 2006, from http://www.cps.ca/ENGLISH/statements/DT/dt95-01.htm#Folic%20Acid%20Fortification.

FAOBioDec: Database of biotechnology in developing countries [Database]. Rome, Italy: Food and Agricultural Organization of the United Nations (FAO). Retrieved September 26, 2006, from http://www.fao.org/biotech/inventory_admin/dep/default.asp.

FAO. (1995). *Micronutrient fortification of food: Technology and quality control* (FAO Food and Nutrition Paper No. 60). Rome, Italy: Author. Retrieved October 15, 2006, from http://www.fao.org/docrep/W2840E/w2840e0b.htm.

Flour Fortification Initiative website. Retrieved December 20, 2007, from http://www.sph.emory.edu/wheatflour/progress.php.

French Academy of Medicine. (2002, December 10). *OGM et santé* [GMO and health]. Recommendations (Alain Rerat). Paris, France: Author.

French Academy of Sciences. (2002, December). *Genetically modified plants* (Report on science and technology No. 13). Paris, France: Author.

GAIN website. Retrieved October 29, 2006, from http://www.gainhealth.org.

HarvestPlus. (2004). *Breeding crops for better nutrition* (Revised April 2006). Washington, DC: International Food Policy Research Initiative (IFPRI). Available on the World Wide Web: http://www.harvestplus.org/pdfs/brochure.pdf.

Helt, H.W. (2004). *Are there hazards for the consumer when eating food from genetically modified plants?* Göttingen, Germany: Universitat Göttingen.

International Service for the Acquisition of Agri-biotech Applications (ISAAA). (2007, July 6). *Crop biotech update*. New York, NY: Author.

International Zinc Nutrition Consultative Group website. Retrieved from http://www.izincg.org/.

Micronutrient Initiative website. Retrieved from http://www.micronutrient.org/.

Morris, C.E., & Sands, D.C. (2006). The breeder's dilemma—Yield or nutrition? *Nature Biotechnology*, *24*(9), 1078-1080.

Mozaffarian, D., Katan, M.B., Ascherio, A., Stampfer, M.D., & Willett, W.C. (2006). Trans fatty acids and cardiovascular disease. *New England Journal of Medicine*, *354*, 1601-1613.

Mutant varieties database [Database]. Vienna, Austria: FAO and International Atomic Energy Agency (IAEA). Retrieved October 29, 2006, from http://www-infocris.iaea.org/MVD/.

Network for Sustained Elimination of Iodine Deficiency website. Retrieved October 2006, from http://206.191.51.240/index.html.

Pew Initiative on Food and Biotechnology. (2001, September). *Harvest on the horizon: Future uses of agricultural biotechnology*. Richmond, VA: Author.

Popkin, B.M. (2001). The nutrition transition and obesity in the developing world. *Journal of Nutrition*, *131*, 871S-873S.

Pray, C. (2006). *The Asian Maize Biotechnology Network (AMBIONET): A model for strengthening national agricultural research systems*. Mexico, DF: CIMMYT.

Qaim, M., Stein, A.J., & Meenakshi, J.V. (2007). Economics of biofortification. In K. Otsuka & K. Kalirajan (Eds.), *Contributions of agricultural economics to critical policy issues*. Malden, MA: Wiley-Blackwell Publishing.

Regmi, A., & Gelhar, M. (2005, February). *New directions in global food markets* (Agriculture Information Bulletin No. 794). Washington, DC: USDA Economic Research Service. Available on the World Wide Web: http://www.ers.usda.gov/publications/aib794/aib794.pdf.

Shekar, M., Heaver, R., Lee, Y. (Eds.). (2006). *Repositioning nutrition as central to development: A strategy for large scale action* (Directions in Development Series). Washington, DC: World Bank.

Smith, L., & Haddad, L. (2000). *Overcoming child malnutrition in developing countries: Past achievements and future choices* (Food, Agriculture, and Environment Discussion Paper No. 30). Washington, DC: IFPRI.

Stein, A.J. (2006). *Micronutrient malnutrition and the impact of modern plant breeding on public health in India: How cost-effective is biofortification?* Göttingen, Germany: Cuvillier Verlag.

United Nations Children's Fund (UNICEF), & The Micronutrient Initiative (MI). (2004). *Vitamin and mineral deficiency: A global damage assessment report*. New York, NY: Author. Retrieved on July 11, 2006 from http://www.weforum.org/pdf/Initiatives/GHI_2004_UNICEF_MI.pdf.

United Nations System, Standing Committee on Nutrition (SCN). (2004, March). *5th report on world nutrition situation: Nutrition for improved development outcomes*. Geneva, Switzerland: Author.

US National Academy of Sciences. (2004). *Safety of genetically engineered foods: Approaches to assessing unintended health effects*. Washington, DC: National Academies Press.

World Health Organization (WHO). (2004). *Iodine status worldwide: WHO global database on iodine deficiency*. Geneva, Switzerland: Author. Available on the World Wide Web: http://whqlibdoc.who.int/publications/2004/9241592001.pdf.

WHO, World Food Programme, & UNICEF. (2007). *Preventing and controlling micronutrient deficiencies in populations affected by an emergency*. Geneva, Switzerland: WHO. Retrieved on December 20, 2007, from http://www.who.int/nutrition/publications/WHO_WFP_UNICEFstatement.pdf.