Genetically Engineered Foods

Biofortification of Staple Food Crops – A Sustainable Solution to Micronutrient Malnutrition?

A Case Study

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Introduction:

A spirited debate on the pros and cons of genetically modified organisms (GMOs) began more than a decade ago and continues unabated to the present time. Scientists, politicians, farmers, seed company executives, food manufacturers, leaders of nongovernmental organizations, and food consumers have all joined the discussion. Many of the scientific and political issues related to GMOs were the subject of a recent conference in New Delhi, India held in May, 2003. The title of this conference was "Indo-US Agricultural Biotechnology Conference on Nutritional Enhancement and Abiotic Stress Tolerance. The following exchange between R.V and P.K. at one of the coffee breaks at the conference illustrates some of the conflicting views that well meaning and highly educated people can have.

R.V.: "P.K., I was moved by Dr. Ganguly's talk, especially when he showed the alarming statistics on the prevalence of nutritional deficiency diseases in children in this country. I believe that the situation is not only alarming, it is inhumane. We must do something and we must do it now. That is why I think we should apply our knowledge and skills in the area of conventional plant breeding programs and chemical fortification to enhance the nutrient content of the food crops consumed by our children. We cannot afford to waste valuable time and limited resources on genetic engineering technologies that are unproven and that may result in foods that are unsafe for human consumption and the environment.

P.K.: "R.V., I think you miss the point. Dr. Ganguly's comments at the conference today make it clear that we need to deliver higher quantities of micronutrients in our rice crops than conventional breeding programs can ever hope to achieve. Transgenic crops are essential to an effective biofortification program. Micronutrient delivery through conventional breeding cannot deliver the levels of nutrients required. Moreover, adding nutrients at food processing plants simply does not work in poor areas where folks rely on subsistence farming for most of their food. Just look at the bleak track record to date. With GMO technology just around the corner, it only makes sense to invest in the research that will see it through to completion. The scientists working on golden rice are frustrated for good reason. Why should the research be brought to a halt after only two lines have been developed? It is widely expected that in line three the genes will express better, delivering much higher vitamin A content in the product."

R.V.: "The research and development that the Challenge grant has supported has established only proof of concept, P.K. As a leader at the Council of Research I should think you of all people would appreciate that there remains a long way to go before viable products are ready for market, and it is another step still to ensure that consumers will buy them. Under the best of circumstances there are still site suitability trials to conduct, in addition to bioavailability tests, then biosafety tests, then consumer acceptability studies. I fear the nutrition and public health communities have developed unrealistic expectations about the state of the genetic technology for enriching crops with iron and beta-carotene. These need to be brought into line with reality."

P.K. "Monsanto does this sort of research for crops sold in the USA, doesn't it, R.V? I do find it quite infuriating that they won't work on transgenic genes for India beyond basic research, simply because our farmers cannot afford to pay their royalties. On the other hand, though, they have given us permission to use the technologies they have developed and patented so that we can produce our own transgenic seeds. Our scientists are able and willing, but cannot seem to get the financial and moral support they need to succeed. It seems clear that the real problem lies with a few insistent ideologists who have mastered the use of fear tactics to keep the public misinformed. They chant on about presumed health and environmental risks of GMOs, while the known risks of nutritional deficiencies are obvious to everyone. These zealots produce no scientific proof to support their claims, yet they have succeeded in convincing the media and the general populace that GM foods are unsafe and bad for the environment. This has made it very difficult for our political leaders to issue policies that would effectively address nutrient deficiency problems. Perhaps our next conference should be on the politics rather than the science of biotechnology's contribution to alleviating hunger and malnutrition in our country. For the time being though, let us return to the session. Maybe something will develop here to help move us out of limbo."

Setting:

<u>Rice growing region in Southern India</u>. Small farmers who cultivate 2 to 4 hectares of land dominate agriculture in the area. The primary crop is rice but pulses and vegetables are also grown. The majority of the population relies almost exclusively on locally grown food. Most families have adequate food to meet calorie needs but iron and vitamin A deficiencies affect more that 50% of the children. Up to 80% of women suffer from nutritional anemia. Birth rates are among the highest in the world.

Problem or Dilemma:

Up to half of the world's population suffers from micronutrient malnutrition due to inadequate intakes of vitamins and minerals. Everyone agrees that we must develop effective strategies for increasing intakes of micronutrients by people in developing countries, especially the poor. The question is, what strategy or strategies will be the most cost effective and the most likely to succeed? Herein lies the dilemma. In an ideal world, every person would have access to a balanced and nutritionally adequate diet made up of a wide variety of foods. Unfortunately, such a diet is beyond the means of hundreds of millions of people and therefore does not offer a realistic solution. A second strategy that has been tried many times is the distribution of dietary supplements (vitamin and mineral pills). This strategy can be very effective in the short term when programs to deliver the supplements are put in place. However, when funding for the programs lapse, people rarely continue taking supplements because of unpleasant side effects, cost, sporadic availability, or complete unavailability of the supplements. A third strategy that is gaining momentum in many developing countries is fortification of staple foods with vitamins and minerals. Fortification of foods has been used successfully in many developed countries for decades and offers many advantages over supplements. A forth strategy that has also gained a lot of attention in recent years is nutritional enhancement of staple food crops using techniques of biotechnology (genetic engineering). Scientists have developed genetically modified rice varieties (GMOs) that contain twice the normal levels of iron and nutritionally significant amounts of beta-carotene, a precursor of vitamin A.

The Indian Minister of Agriculture has studied these and other options and must decide soon on which strategy to pursue as her government struggles to address the widespread problem of micronutirent deficiency diseases in the Indian population. This will not be an easy decision since the wrong choice could have a far-reaching impact on the health of millions of Indians not to mention severe political consequences for the government. To make it even more difficult, activists, including Greenpeace and several local organizations, have mounted a public campaign in opposition to GMO foods.

Facts and Background:

Global food supplies per person are at an all-time high and are sufficient to satisfy the calorie needs of every person on earth. However, the supply of micronutrients (vitamins and minerals) falls far short of meeting the requirements of up to ½ of the world population. Recent estimates are that 2 billion people are iron deficient, 250 million suffer from vitamin A deficiency, and unknown millions are zinc deficient. Consequences of these and other deficiencies include high rates of infant mortality, increased susceptibility to infectious diseases, reduced worker productivity, and permanent stunting of cognitive and physical development in children. Causes of these nutrient deficiencies are multiple but a shift toward increased planting of "Green Revolution" crops (wheat, rice, and maize) at the expense of more nutrient dense crops such as legumes and vegetables is a major factor. Nutrient enhancement of staple crops has the potential to dramatically reduce prevalences of these nutrient deficiency diseases.

One strategy for nutritional enhancement is biofortification. This approach uses genetic engineering to develop transgenic varieties of crop plants that have increased concentrations of iron, vitamin A (e.g. "golden rice"), and other nutrients. Presumably, the enhanced levels of nutrients will be sustainable as long as the crop varieties are available to farmers. Moreover, biofortification is more cost effective than traditional food fortification technologies, which require the addition of nutrients to every batch of product during processing. Improving the nutritional status of populations is critical for sustainable development because people who are well nourished have smaller families, are more productive, and have the time and energy to devote to environmental conservation and other sustainability issues. However, many activist groups (e.g. Greenpeace) are adamantly opposed to these so-called "Frankenfoods" for a variety of reasons.

Conventional Plant Breeding. Agriculture began some 10,000 years ago in an area known as the Fertile Crescent in present day Iraq. Gradually, food from agriculture production replaced foods obtained by hunting wild animals and gathering plants. Today, hunter-gatherers make up only a tiny minority of the world's population and people rely almost exclusively on agriculture for their food. Modern domestic animals and food crops had their origin in wild animals and plants. Most of us would not recognize the wild precursors of these crops because they have changed so dramatically over the years. For example, figure 1 shows a modern ear of corn on the left and teosinte, its wild ancestor, on the right. Centuries ago, Native Americans used selective breeding to create the corn they were growing when the Europeans first came to the Americas. Virtually all of today's food crops have been genetically modified to improve resistance to pests and diseases, increase the size of the edible portion, reduce concentrations of toxic chemicals, enhance flavor and color, etc. Either natural selection or selective breeding by humans achieved most of this genetic modification. Natural selection is a process where a plant or animal that is more resistant to a disease, pest, or other environmental stress survives while closely related varieties disappear. Selective plant breeding by humans is a process where farmers or agricultural scientists make sexual crosses between two related plant varieties to obtain a new plant that includes desirable characteristics of both of its parents, for example improved yield, disease resistance, or some other trait. This is a slow and tedious process because the new plant inherits half of its genes from one parent and half from the other and most likely expresses some undesirable traits along with the desirable ones. Plant breeders must make further crosses to try to eliminate the undesirable traits. Moreover, only closely related plants can be crossed, making it almost impossible to introduce a desirable trait from a plant of another species or from a bacterium (Shelton et al, 2002).

The Green Revolution. In spite of the limitations of conventional plant breeding, plant scientists have made remarkable progress in improving the agronomic characteristics of plants. In the late 1950's, they began a concerted effort to develop new, higher yielding varieties of rice and wheat. Conventional cross breeding technologies were used to introduce dwarfing genes into the plants. The resulting crosses had shorter, stiffer stems and therefore could direct more energy toward producing seeds and less to producing stems and leaves. Because yields from these new varieties (now called modern varieties or MV) were substantially higher than from currently available varieties, farmers in many parts of the world quickly adopted them. Dr. Norman Borlaug, a plant breeder at the International Center for Wheat and Maize Improvement (CIMMYT) in Mexico received the Nobel Peace Prize in 1970 for his work in developing and promoting these modern varieties of cereal grains. Recent estimates of the impact of the Green Revolution indicate that per capita calorie intakes in the developing world would be 13.3 to 14.4 % lower today if Green Revolution varieties had not been adopted by farmers in these regions (Evenson and Gollin, 2003). Moreover, the Green Revolution is credited with helping India go from an importer of cereal grains to self-sufficiency and even a surplus of food during the period between 1961 and 2000 in spite of a more than doubling of the population over the same period.

While most observers would agree that the Green Revolution has had a tremendously positive impact on world protein and calorie supplies, it has not delivered adequate levels of micronutrients (vitamins and minerals). Farmers have shifted their production toward the high yielding cereal crops and away from more nutrient dense crops like legumes and vegetables (Graham et al., 2001). As a result, prevalences of micronutrient deficiencies, especially iron deficiency, have actually increased in some developing countries.

Figure 1. Left: ear of a modern corn variety. Right: Teosinte, a wild plant used by Native Americans to create the corn they used in agriculture.

<u>Agricultural Biotechnology.</u> Agricultural biotechnology refers to the use of techniques of modern biology to modify living organisms or components of living organisms to produce products with specific benefits or develop crops that are more resistant to diseases, pests, or environmental stresses. It often involves genetic engineering (see below) and the products may be called genetically modified organisms (GMOs) or genetically engineered organisms. Most of the GMOs we read about are products of genetic engineering.

About 30 years ago, Stanley Cohen and Herbert Boyer developed techniques for transferring single genes from one organism to another. Their discoveries launched a new field of science that we now call genetic engineering. **Genetic engineering is a technique for inserting one or a few genes from one organism into the DNA of a second organism.** It differs from traditional plant breeding in two important ways. First, it allows scientists to insert genes from unrelated species into plants and animals. For example, Bt corn contains a gene from a bacterium called *Bacillus thruingiensis*. This gene codes for a protein that is toxic to certain insects that may cause damage to the corn plant, giving the plant the ability to defend itself against the insect. **Plants or animals that contain genes from another species are called transgenic.** Second, the amount of genetic material that is transferred with genetic engineering is much smaller than the amount transferred in traditional plant or animal breeding. This reduces the likelihood that an undesirable trait will be transferred along with the desired trait and therefore dramatically speeds up the process of developing crops with improved traits (Shelton et al, 2002).

Pros and Cons of Agricultural Biotechnology. Biotech foods were first introduced into the U.S. market in 1990 and today up to 70% of processed foods sold in the U.S. contain at least one ingredient from a genetically engineered plant (Shelton et al., 2002). The majority of these ingredients are derived from either Bt corn or herbicide tolerant soybeans. Proponents of agricultural biotechnology argue that engineered crops have reduced pesticide use in agriculture (crops such as Bt corn contain their own natural pesticide), reduced soil erosion (weeds in fields of herbicide tolerant soybeans can be controlled by one application of a herbicide, thereby reducing the need to control weeds by mechanical cultivation), improved the safety of foods (maize plants infested with the European corn borer produce more fumonisin, a potential carcinogen; the European corn borer cannot grow in Bt corn.), and improved yields (Falk et al., 2002). Opponents argue that genetically engineered crops may lead to "super weeds" when genes form herbicide resistant crops drift into wild plants, may contain allergens, may harm non-target insects, and may cause unknown health problems. Also, organic farmers worry than pollen from a neighbor's GM crop may drift to their crop, thereby making the crop unacceptable for sale as organic food. Some people oppose genetic engineering on a religious and ethical basis. They feel that genetic engineers are playing God. Greenpeace, a well-known advocacy organization has been especially vocal in opposing GMOs. One example of their strong opposition was an action in February 2003 to block the entrance to a supermarket in Massachusetts. In a press release at the time of the action, Greenpeace stated: "Tens of thousands of Shaw's customers have demanded that their food no longer contain these genetic experiments, but Shaw's has ignored them," said Heather Whitehead, Campaigner with the Greenpeace Genetic Engineering Campaign. "Shaw's won't stop the flow of genetically engineered food to its stores, so Greenpeace activists will." (http://www.truefoodnow.org/inside_scoop/inthenews.html)

Rice. Rice is a major staple food for the majority of the world's population. In some areas of Asia, it provides more than two thirds of total caloric intake (Dawe et al., 2002). Most of the rice that is consumed is polished to remove the bran and germ layers of the kernel, leaving the white endosperm, which is composed mainly of starch and protein. The endosperm contains no beta-carotene (a precursor to vitamin A) and only low levels of many other essential vitamins and minerals (see table 1). In the U.S., white rice is enriched (fortified) with iron, riboflavin, niacin, and folic acid to replace some of the nutrients lost during the milling process. Brown rice is rarely fortified.

Table 1. Content of selected nutrients in 1 cup (about 160 grams) of cooked rice.

	Brown Rice[1]	White Rice[1] (unenriched)	GM Rice (Golden)[2]	GM Rice (iron rich)[3]	White Rice[1] (enriched)
Calories	216	205			205
Protein (g)	5.0	4.2			4.2
Iron (mg)	0.8	0.3		0.7	1.9
Zinc (mg)	1.2	0.8			0.8
Vit A (μgRAE)	0.0	0.0	127		0.0

[1] USDA Nutrient Database, 2003
[2] Transgenic Golden Rice, Paine et al., 2005
[3] Transgenic iron-rich rice, Vasconcelos et al, 2003

Golden Rice. Recently, an effort was launched to introduce genes from daffodils and the bacterium *Erwinia uredovora* into rice that code for the synthesis of enzymes required for beta-carotene synthesis (Beyer et al., 2002). The transgenic rice contained a level of beta-carotene equal to about 8 retinol activity equivalents (μg RAE) per cup of cooked rice. This is low compared to the RDAs for vitamin A, which range from 300 to 900 μg RAE per day for young children and adult males, respectively. In 2005, a group from Syngenta in the U.K. developed “Golden Rice 2” using genes from maize rather than daffodils. Golden Rice 2 contains up to 127 μg RAE per cup of cooked rice. Current intakes of vitamin A by children in many developing countries are below 200 RAE per day. Therefore, high intakes of golden rice could significantly increase vitamin A intake, especially among children with very low intakes (Dawe, 2002).

Iron-rich Rice. The RDA for iron ranges from 7 mg/day for young children to 18 mg/day for women of child-bearing age. Therefore, when unenriched, polished rice is the major staple in the diet, high prevalences of iron deficiency should not be surprising. Recently, there have been several reports of transgenic rice varieties with enhanced levels of iron in the endosperm. This is accomplished by inserting a ferritin gene from soybeans into the rice genome. Ferritin is an iron storage protein found in plants and animals but not in the endosperm of cereal grains. Vasconcelos et al. (2003) were able to double the iron content of the endosperm of indica rice, a variety popular in many rice-eating regions of the world. While the iron content of these transgenic rice grains is still low, it is likely to have a beneficial effect in populations consuming large quantities of rice.

Food Fortification

Food fortification may be defined as the addition of nutrients to foods for the purpose of preventing nutrient deficiencies in populations. Food fortification in the U.S. began in the 1920s with the addition of iodine to salt. In the 1930s vitamin D was added to milk to prevent rickets. Fortification of flour and cereal products with iron, riboflavin, niacin, and thiamin was implemented in the 1940s and folic acid was added to the list for these products in the 1990s. The technology for adding nutrients to foods is well developed and fortification is one of the most cost-effective public health interventions available (Darnton-Hill and Nalubola, 2002). Several criteria must be met for successful fortification programs (FAO, 1996). They are listed in table 1.

Table 1. Criteria for fortification of foods (FAO, 1996)

- The food vehicle must be consumed by the target population
- The fortified food must be consumed on a regular basis, preferably with most meals
- Adding the nutrient (or nutrients) to the food should not change the color, flavor, or shelf life of the food
- Fortification should not appreciably increase the cost of the food to the consumer
- The food to be fortified should be centrally processed

While the technology for adding nutrients to foods is well developed and has been successfully implemented in industrialized countries, transfer of the technology to developing countries poses many challenges. Rice is especially difficult to fortify because the fortificants must be applied as a coating on the surface of the kernels. Fortifying flours is much simpler because the nutrients that are available in powdered form can simply be mixed into the flour. Coating mixtures containing iron and other nutrients have been developed for rice fortification (Mannar and Gallego, 2002). These have been reasonably successful but losses during washing, cooking, and storage remain relatively high.

Protagonist: The Indian Minister of Agriculture.

Stakeholders: Subsistence farmers in India and their families.

Moral and Ethical Issues: Agricultural biotechnology, with its implications for human health, the environment, and food production, raises several ethical dilemmas. To put these dilemmas in context, it is helpful to recall the United Nation's Universal Declaration of Human Rights, which was issued in 1948. Article 25 of that Declaration states that "everyone has the right to a standard of living adequate for the health and well-being of himself and his family, including food...". This article is widely interpreted to mean that access to an adequate and nutritionally balanced diet is a basic human right. If we accept and agree with this interpretation, then we must accept some responsibility as students, teachers, scientists, and citizens of the world for extending this human right to everyone on the planet. This requires that we address several important moral and ethical issues including the following:

- The application of agricultural biotechnology may cause environmental damage, including loss of biodiversity. Is biotechnology therefore morally wrong even if its application improves accessibility to food?

- Agricultural biotechnology may be an important tool in efforts to increase crop yields, improve the nutritional value of foods, and generally to provide the world's billions with a more adequate and nutritionally complete food supply. Are actions by opponents of biotechnology, therefore, morally wrong because they increase suffering and death among the poorest of the world's poor?
- New technologies developed through scientific research almost always carry some risk. Do the potential benefits of agricultural biotechnology outweigh possible risks? Who should bear the risks and who should receive the benefits?
- Some would argue that genetic engineering is, in effect, tampering with God's creation. Is genetic engineering, therefore, in conflict with some religious beliefs?

Practical and Economic Issues:

- Many populations around the world are accustomed to highly polished, pure white rice. Will people therefore avoid Golden Rice because of its yellow color even if they know it is more nutritious for them and their children?
- Some countries refuse to allow imports of genetically engineered crops because of perceived negative impacts on human health and the environment. Therefore, farmers who plant GM seeds may be cutting themselves off from lucrative export markets. This being the case, are governments justified in banning GM crops in their respective countries?

Decision to be made: The minister of agriculture must decide whether to allocate limited resources and political capital toward gaining approval of and distributing nutritionally enhanced transgenic rice to poor farmers or to use the funds to mount a national food fortification program using proven technologies currently in use in developed countries such as the U.S.

Glossary

Agricultural biotechnology: Technology based on the use of techniques of modern biology to modify living organisms or components of living organisms to produce products with specific benefits or develop crops that are more resistant to diseases, pests, or environmental stresses.

Bacillus thuringiensi (Bt): A bacterium found naturally in the soil. It produces a protein called *Bt toxin* that is toxic to certain insects when they ingest it. The gene for *Bt toxin* has been transferred using tools of genetic engineering to several important crops, including corn and cotton, to make them toxic to common insect pests.

Biotechnology: The use of biological organisms in any technological application. Examples include using yeast to make bread and wine, bacteria to make yogurt and cheese, herbicide tolerant soybeans to permit the application of the herbicide glyphosate (Roundup®) without killing the soybean plant.

Food fortification: The addition of nutrients to foods during processing for the purpose of preventing nutrient deficiencies in populations.

Gene: A functional segment of a DNA molecule made up of nucleotides arranged in a specific sequence. Genes encode for specific proteins or RNA molecules.

Genetic Engineering: A subset of biotechnology. Organisms are "engineered" by transferring DNA from another organism or by modifying the DNA in the existing organism. Organisms may be engineered to produce desirable enzymes, become resistant to insects, develop greater tolerance to drought, etc.

Genetically modified Organism (GMO).   Commonly recognized as organisms that have been modified by inserting a gene from one organism into another using genetic engineering. Many scientists prefer GEO (*genetically engineering organism)* to GMO because, technically, GMOs include organisms developed through conventional plant or animal breeding as well as through genetic engineering.

Green Revolution: An agricultural revolution begun in the 1950's that developed new higher yielding varieties of wheat and rice through conventional plant breeding and promoted their distribution to and adoption by farmers around the world. This revolution is widely credited with preventing famines in south Asia and other regions by dramatically increasing yields of rice and wheat.

Glyphosate surfactant herbicide (GlySH): The most widely used general purpose herbicide in the world. It is a broad spectrum herbicide and will kill most plants. It kills by disrupting the shikimic acid pathway, a pathway involved in amino acid metabolism in plants and bacteria but not in animals. It is less toxic to mammals (including people) than the organophosphate herbicides, which are neurotoxins.

Herbicide-tolerant crop: Crops that have been genetically modified to tolerate the application of certain herbicides that farmers may use to control weeds.   The most common example is Roundup® Ready Soybeans. These soybeans have been genetically modified to be tolerant to the herbicide glyphosate.

Mutation breeding: The application of chemicals or ionizing radiation to whole organisms to produce changes in their DNA (mutations) in the hope that these changes will confer beneficial traits to the organism, e.g. disease or pest resistance.

Natural selection: A process where a plant or animal that is more resistant to a disease, pest, or other environmental stress survives while closely related varieties disappear.

Selective breeding: Genetic modification of plants or animals by making crosses between two closely related organisms (members of the same species) to obtain a new organism with desirable traits from its two parents.

Substantial equivalence: The guiding principle for safety assessment of genetically engineered foods. The genetically engineered food is compared to its conventional counterpart and if there are no substantial differences between the two, the GE food is declared safe. Criteria for comparison include agronomic characteristics, composition (nutrients, antinutrients, toxicants, potential allergens), and phenotypic traits (color, texture, etc.).

Traditional Breeding Methods: Methods designed to genetically modify plants and animals that have been used for many years. These methods include selective breeding, mutation breeding, and/or tissue culture

Transgenic: An organism that contains one or more genes (DNA sequences) from an organism of another species. For example, Bt corn contains a gene from the bacterium *Bacillus thuringeniensis*.

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Relevant Web Sites:

Golden Rice Humanitarian Board & Network:
http://www.goldenrice.org/index.html

Union of Concerned Scientists
http://www.ucsusa.org/food_and_environment/genetic_engineering/