Genetically Modified Organisms (GMOs): Transgenic Crops and Recombinant DNA Technology

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If you could save lives by producing vaccines in transgenic bananas, would you? In the debate over large-scale commercialization and use of GMOs, where should we draw the line?

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People have been altering the genomes of plants and animals for many years using traditional breeding techniques. Artificial selection for specific, desired traits has resulted in a variety of different organisms, ranging from sweet corn to hairless cats. But this artificial selection, in which organisms that exhibit specific traits are chosen to breed subsequent generations, has been limited to naturally occurring variations. In recent decades, however, advances in the field of genetic engineering have allowed for precise control over the genetic changes introduced into an organism. Today, we can incorporate new genes from one species into a completely unrelated species through genetic engineering, optimizing agricultural performance or facilitating the production of valuable pharmaceutical substances. Crop plants, farm animals, and soil bacteria are some of the more prominent examples of organisms that have been subject to genetic engineering.

Current Use of Genetically Modified Organisms

Agricultural plants are one of the most frequently cited examples of genetically modified organisms (GMOs). Some benefits of genetic engineering in agriculture are increased crop yields, reduced costs for food or drug production, reduced need for pesticides, enhanced nutrient composition and food quality, resistance to pests and disease, greater food security, and medical benefits to the world's growing population. Advances have also been made in developing crops that mature faster and tolerate aluminum, boron, salt, drought, frost, and other environmental stressors, allowing plants to grow in conditions where they might not otherwise flourish (Table 1; Takeda & Matsuoka, 2008). Other applications include the production of nonprotein (bioplastic) or nonindustrial (ornamental plant) products. A number of animals have also been genetically engineered to increase yield and decrease susceptibility to disease. For example, salmon have been engineered to grow larger (Figure 1) and mature faster (Table 1), and cattle have been enhanced to exhibit resistance to mad cow disease (United States Department of Energy, 2007).

Figure 1

Table 1: Examples of GMOs Resulting from Agricultural Biotechnology

Genetically Conferred Trait	**Example Organism**	**Genetic Change**
APPROVED COMMERCIAL PRODUCTS		
Herbicide tolerance	Soybean	Glyphosate herbicide (Roundup) tolerance conferred by expression of a glyphosate-tolerant form of the plant enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) isolated from the soil bacterium *Agrobacterium tumefaciens*, strain CP4
Insect resistance	Corn	Resistance to insect pests, specifically the European corn borer, through expression of the insecticidal proteinCry1Ab from *Bacillus thuringiensis*
Altered fatty acid composition	Canola	High laurate levels achieved by inserting the gene for ACP thioesterase from the California bay tree *Umbellularia californica*
Virus resistance	Plum	Resistance to plum pox virus conferred by insertion of a coat protein (CP) gene from the virus
PRODUCTS STILL IN DEVELOPMENT		
Vitamin enrichment	Rice	Three genes for the manufacture of beta-carotene, a precursor to vitamin A, in the endosperm of the rice prevent its removal (from husks) during milling
Vaccines	Tobacco	Hepatitis B virus surface antigen (HBsAg) produced in transgenic tobacco induces

		immune response when injected into mice
Oral vaccines	Maize	Fusion protein (F) from Newcastle disease virus (NDV) expressed in corn seeds induces an immune response when fed to chickens
Faster maturation	Coho salmon	A type 1 growth hormone gene injected into fertilized fish eggs results in 6.2% retention of the vector at one year of age, as well as significantly increased growth rates

The pharmaceutical industry is another frontier for the use of GMOs. In 1986, human growth hormone was the first protein pharmaceutical made in plants (Barta *et al*., 1986), and in 1989, the first antibody was produced (Hiatt *et al*., 1989). Both research groups used tobacco, which has since dominated the industry as the most intensively studied and utilized plant species for the expression of foreign genes (Ma *et al*., 2003). As of 2003, several types of antibodies produced in plants had made it to clinical trials. The use of genetically modified animals has also been indispensible in medical research. Transgenic animals are routinely bred to carry human genes, or mutations in specific genes, thus allowing the study of the progression and genetic determinants of various diseases.

Potential GMO Applications

Many industries stand to benefit from additional GMO research. For instance, a number of microorganisms are being considered as future clean fuel producers and biodegraders. In addition, genetically modified plants may someday be used to produce recombinant vaccines. In fact, the concept of an oral vaccine expressed in plants (fruits and vegetables) for direct consumption by individuals is being examined as a possible solution to the spread of disease in underdeveloped countries, one that would greatly reduce the costs associated with conducting large-scale vaccination campaigns. Work is currently underway to develop plant-derived vaccine candidates in potatoes and lettuce for hepatitis B virus (HBV), enterotoxigenic *Escherichia coli* (ETEC), and Norwalk virus. Scientists are also looking into the production of other commercially valuable proteins in plants, such as spider silk protein and polymers that are used in surgery or tissue replacement (Ma *et al*., 2003). Genetically modified animals have even been used to grow transplant tissues and human transplant organs, a concept called xenotransplantation. The rich variety of uses for GMOs provides a number of valuable benefits to humans, but many people also worry about potential risks.

Risks and Controversies Surrounding the Use of GMOs

Despite the fact that the genes being transferred occur naturally in other species, there are unknown consequences to altering the natural state of an organism through foreign gene expression. After all, such alterations can change the organism's metabolism, growth rate, and/or response to external environmental factors. These consequences influence not only the GMO itself, but also the natural environment in which that organism is allowed to proliferate. Potential health risks to humans include the possibility of exposure to new allergens in genetically modified foods, as well as the transfer of antibiotic-resistant genes to gut flora.

Horizontal gene transfer of pesticide, herbicide, or antibiotic resistance to other organisms would not only put humans at risk, but it would also cause ecological imbalances, allowing previously innocuous plants to grow uncontrolled, thus promoting the spread of disease among both plants and animals. Although the possibility of horizontal gene transfer between GMOs and other organisms cannot be denied, in reality, this risk is considered to be quite low. Horizontal gene transfer occurs naturally at a very low rate and, in most cases, cannot be simulated in an optimized laboratory environment without active modification of the target genome to increase susceptibility (Ma *et al*., 2003).

In contrast, the alarming consequences of vertical gene transfer between GMOs and their wild-type counterparts have been highlighted by studying transgenic fish released into wild populations of the same species (Muir & Howard, 1999). The enhanced mating advantages of the genetically modified fish led to a reduction in the viability of their offspring. Thus, when a new transgene is introduced into a wild fish population, it propagates and may eventually threaten the viability of both the wild-type and the genetically modified organisms.

Unintended Impacts on Other Species: The Bt Corn Controversy

One example of public debate over the use of a genetically modified plant involves the case of Bt corn. Bt corn expresses a protein from the bacterium *Bacillus thuringiensis*. Prior to construction of the recombinant corn, the protein had long been known to be toxic to a number of pestiferous insects, including the monarch caterpillar, and it had been successfully used as an environmentally friendly insecticide for several years. The benefit of the expression of this protein by corn plants is a reduction in the amount of insecticide that farmers must apply to their crops. Unfortunately, seeds containing genes for recombinant proteins can cause unintentional spread of recombinant genes or exposure of non-target organisms to new toxic compounds in the environment.

The now-famous Bt corn controversy started with a laboratory study by Losey *et al*. (1999) in which the mortality of monarch larvae was reportedly higher when fed with milkweed (their natural food supply) covered in pollen from transgenic corn than when fed milkweed covered with pollen from regular corn. The report by Losey *et al*. was followed by another publication (Jesse & Obrycki, 2000) suggesting that natural levels of Bt corn pollen in the field were harmful to monarchs.

Debate ensued when scientists from other laboratories disputed the study, citing the extremely high concentration of pollen used in the laboratory study as unrealistic, and concluding that migratory patterns of monarchs do not place them in the vicinity of corn during the time it sheds pollen. For the next two years, six teams of researchers from government, academia, and industry investigated the issue and concluded that the risk of Bt corn to monarchs was "very low" (Sears *et al*., 2001), providing the basis for the U.S. Environmental Protection Agency to approve Bt corn for an additional seven years.

Unintended Economic Consequences

Another concern associated with GMOs is that private companies will claim ownership of the organisms they create and not share them at a reasonable cost with the public. If these claims are correct, it is argued that use of genetically modified crops will hurt the economy and environment, because monoculture practices by large-scale farm production centers (who can afford the costly seeds) will dominate over the diversity contributed by small farmers who can't afford the technology. However, a recent meta-analysis of 15 studies reveals that, on average, two-thirds of the benefits of first-generation genetically modified crops are shared downstream, whereas only one-third accrues upstream (Demont *et al*., 2007). These benefit shares are exhibited in both industrial and developing countries. Therefore, the argument that private companies will not share ownership of GMOs is not supported by evidence from first-generation genetically modified crops.

GMOs and the General Public: Philosophical and Religious Concerns

In a 2007 survey of 1,000 American adults conducted by the International Food Information Council (IFIC), 33% of respondents believed that biotech food products would benefit them or their families, but 23% of respondents did not know biotech foods had already reached the market. In addition, only 5% of those polled said they would take action by altering their purchasing habits as a result of concerns associated with using biotech products.

According to the Food and Agriculture Organization of the United Nations, public acceptance trends in Europe and Asia are mixed depending on the country and current mood at the time of the survey (Hoban, 2004). Attitudes toward cloning, biotechnology, and genetically modified products differ depending upon people's level of education and interpretations of what each of these terms mean. Support varies for different types of biotechnology; however, it is consistently lower when animals are mentioned.

Furthermore, even if the technologies are shared fairly, there are people who would still resist consumable GMOs, even with thorough testing for safety, because of personal or religious beliefs. The ethical issues surrounding GMOs include debate over our right to "play God," as well as the introduction of foreign material into foods that are abstained from for religious reasons. Some people believe that tampering with nature is intrinsically wrong, and others maintain that inserting plant genes in animals, or vice versa, is immoral. When it comes to genetically modified foods, those who feel strongly that the development of GMOs is against nature or religion have called for clear labeling rules so they can make informed selections when choosing which items to purchase. Respect for consumer choice and assumed risk is as important as having safeguards to prevent mixing of genetically modified products with non-genetically modified foods. In order to determine the requirements for such safeguards, there must be a definitive assessment of what constitutes a GMO and universal agreement on how products should be labeled.

These issues are increasingly important to consider as the number of GMOs continues to increase due to improved laboratory techniques and tools for sequencing whole genomes, better processes for cloning and transferring genes, and improved understanding of gene expression systems. Thus, legislative practices that regulate this research have to keep pace. Prior to permitting commercial use of GMOs, governments perform risk assessments to determine the possible consequences of their use, but difficulties in estimating the impact of commercial GMO use makes regulation of these organisms a challenge.

History of International Regulations for GMO Research and Development

In 1971, the first debate over the risks to humans of exposure to GMOs began when a common intestinal microorganism, *E. coli*, was infected with DNA from a tumor-inducing virus (Devos *et al*., 2007). Initially, safety issues were a concern to individuals working in laboratories with GMOs, as well as nearby residents. However, later debate arose over concerns that recombinant organisms might be used as weapons. The growing debate, initially restricted to scientists, eventually spread to the public, and in 1974, the National Institutes of Health (NIH) established the Recombinant DNA Advisory Committee to begin to address some of these issues.

In the 1980s, when deliberate releases of GMOs to the environment were beginning to occur, the U.S. had very few regulations in place. Adherence to the guidelines provided by the NIH was voluntary for industry. Also during the 1980s, the use of transgenic plants was becoming a valuable endeavor for production of new pharmaceuticals, and individual companies, institutions, and whole countries were beginning to view biotechnology as a lucrative means of making money (Devos *et al*., 2007). Worldwide commercialization of biotech products sparked new debate over the patentability of living organisms, the adverse effects of exposure to recombinant proteins, confidentiality issues, the morality and credibility of scientists, the role of government in regulating science, and other issues. In the U.S., the Congressional Office of Technology Assessment initiatives were developed, and they were eventually adopted worldwide as a top-down approach to advising policymakers by forecasting the societal impacts of GMOs.

Then, in 1986, a publication by the Organization for Economic Cooperation and Development (OECD), called "Recombinant DNA Safety Considerations," became the first intergovernmental document to address issues surrounding the use of GMOs. This document recommended that risk assessments be performed on a case-by-case basis. Since then, the case-by-case approach to risk assessment for genetically modified products has been widely accepted; however, the U.S. has generally taken a product-based approach to assessment, whereas the European approach is more process based (Devos *et al*., 2007). Although in the past, thorough regulation was lacking in many countries, governments worldwide are now meeting the demands of the public and implementing stricter testing and labeling requirements for genetically modified crops.

Increased Research and Improved Safety Go Hand in Hand

Proponents of the use of GMOs believe that, with adequate research, these organisms can be safely commercialized. There are many experimental variations for expression and control of engineered genes that can be applied to minimize potential risks. Some of these practices are already necessary as a result of new legislation, such as avoiding superfluous DNA transfer (vector sequences) and replacing selectable marker genes commonly used in the lab (antibiotic resistance) with innocuous plant-derived markers (Ma *et al*., 2003). Issues such as the risk of vaccine-expressing plants being mixed in with normal foodstuffs might be overcome by having built-in identification factors, such as pigmentation, that facilitate monitoring and separation of genetically modified products from non-GMOs. Other built-in control techniques include having inducible promoters (e.g., induced by stress, chemicals, etc.), geographic isolation, using male-sterile plants, and separate growing seasons.

GMOs benefit mankind when used for purposes such as increasing the availability and quality of food and medical care, and contributing to a cleaner environment. If used wisely, they could result in an improved economy without doing more harm than good, and they could also make the most of their potential to alleviate hunger and disease worldwide. However, the full potential of GMOs cannot be realized without due diligence and thorough attention to the risks associated with each new GMO on a case-by-case basis.