Biotech foods: A closed and reopened case

George R. Oliver
James E. Gibson
Jeffrey D. Wolt
Diane M. Shanahan

Biotechnology is an exciting new area of science that promises tremendous benefits for people throughout the world. This new technology may provide a wide range of superior products: foods with increased nutritional content, crops that can protect themselves against pests and disease, drugs and vaccines, and industrial materials made from renewable resources (1). As with the introduction of any new technology, biotechnology has generated enthusiasm and concern.

Any product available in the marketplace—especially products that people consume or come into direct contact with—must be determined to be safe and must be regulated by the appropriate agencies. This fundamental requirement applies to all kinds of products, from cars to pharmaceuticals. Although biotech foods have been studied and reviewed extensively, the issues surrounding them involve a complex mix of science, politics, and emotion, thus making it particularly challenging to satisfy the critics. Safety evaluations, part of the overall development process, are critical for ensuring the success of any new biotech product in the marketplace.

Biotech crops have arrived

Biotech or genetically modified crops are produced by modern recombinant DNA technology. Biotech crops were first introduced commercially in the United States in 1993. Because of the financial and management advantages biotech crops offer farmers, they have grown in popularity. In 1999, about 70 million acres of biotech crops were planted.
The National Research Council (NRC) Committee on Genetically Modified Pest-Protected Plants (2) recently reported that risks associated with biotech plants are not significantly different in principle from the kinds of risks associated with conventionally bred crop varieties. The committee also concluded that there was no evidence that biotech foods currently on the market are unsafe.

Following a series of hearings, the U.S. House of Representatives Committee on Science, Subcommittee on Basic Research, recently reported that extensive evaluation worldwide has produced no evidence to support claims that the current biotech crops are a threat to human health or the environment (3). Representative Nick Smith (R-MI), who chaired the subcommittee, answered a resounding “yes” to three basic questions:

- Are agricultural biotechnology and classical breeding methods conceptually the same?
- Are these products safe to eat? and
- Are they safe for the environment?

Such conclusions do not eliminate the need for continued, rigorous, science-based assessment of potential risks. The NRC supports the continued growth and development of a regulatory system with a strong science base.

Despite evidence of the safety of these products, concerns over potential risks remain. Some of the controversy has arisen from misconceptions about this new technology, perhaps fueled by the dissemination of scientific rumor (4). Some of these misconceptions are detailed in the box, “Common misconceptions about biotech crops”. Successful commercialization of any new biotech product is directly related to dispelling public misconceptions. The complex nature of the debate over the safety of biotech crops demands risk analysis that inte-

- Evaluating risk

Addressing the safety issues for biotech crops requires a multifaceted risk-analysis approach that encompasses the assessment, management, and communication of risks, as well as how risks are perceived and compared (5). Fundamental to this analysis is a clear definition and understanding of risk (6). In this context, risk can be thought of as the possibility of undesirable event occurring. Risk analysis allows for science-based assessment to be integrated with social, cultural, economic, and political considerations by acknowledging these varied perspectives throughout the process. In addition to enforcing laws and regulations resulting from scientifically based risk analysis, federal regulatory agencies such as the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), and the U.S. Department of Agriculture (USDA) must be responsible for communicating risk in decision making and implementation.

<table>
<thead>
<tr>
<th>Concern</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingestion of transgenic DNA is harmful to humans or animals.</td>
<td>DNA is present in all biological material and is part of all food. Transgenic DNA is no different from naturally occurring DNA, which has been part of our food since the dawn of time. There is no evidence that DNA in our food causes adverse effects on humans or animals.</td>
</tr>
<tr>
<td>Bt crops adversely affect soil organisms.</td>
<td>Because Bacillus thuringiensis (Bt) is a common soil organism, insecticidally active Bt proteins already occur naturally in the soil. Studies with viable soils show Bt protein is not persistent in soil and, at levels much higher than those found in biotech crop residues, does not adversely affect soil organisms such as earthworms.</td>
</tr>
<tr>
<td>Genes from transgenic crops will create superweeds.</td>
<td>Determination of the chance of transgenes moving from the biotech crop to a weedy relative and creating a superweed is part of the regulatory safety evaluation. Before any new biotech crop is approved for release, there must be evidence to show that the chance of transgene movement to a weed is remote, or, if it occurs, that weeds containing the transgene can be effectively controlled by existing weed control methods.</td>
</tr>
</tbody>
</table>
Risk is not attributable to some potential toxicological effect alone. It is a function of toxicity (hazard) and exposure. An example is the well-publicized debate over the risk of harm to the monarch butterfly when it is exposed to genetically modified corn that produces a natural pesticide originating from the bacterium *Bacillus thuringiensis* (Bt). Concern arose because of a preliminary finding that some young monarch caterpillars died after eating milkweed dusted with pollen from Bt corn in a laboratory study (7).

Although this laboratory test identified Bt corn pollen only as a potential hazard, it was mistakenly interpreted by some as equaling an unacceptable level of risk. Subsequent examination of the monarch's potential exposure has shown that pollen levels are highest in cornfields where milkweed, the target food for the monarch, is less prevalent because of weed control, and therefore the young caterpillars are scarce. The butterflies are more likely to be found outside the crop area, and because pollen levels diminish quickly with distance from the field, the chance for exposure is greatly reduced (4). Although a toxicological hazard to the caterpillars may exist from ingestion of the pollen, exposure, which is the second part of the risk equation, is low, so the actual risk is small.

**Regulation**

Although some critics claim that biotech crops are not adequately studied or regulated, these crops are highly regulated, and an extensive database of safety issues is required. The principles and practices for assessing the risks of biotech crops are already well established in most member countries of the Organization for Economic Cooperation and Development and many emerging countries (8). In the United States, three federal agencies and five laws are involved in the regulation of biotech crops (see box, "U.S. regulation of biotech crops", for details on the agencies and the laws they enforce).

In 1986, the Coordinated Framework for the Regulation of Biotechnology used existing legislation to apportion regulation of biotech products among USDA, EPA, and FDA. The NRC committee recently concluded that these three agencies have been working successfully under this coordinated framework in applying existing statutes to regulate the introduction of biotech pest-protected plants (2), but the committee also noted that there is room for further improvement as the science advances. As with any emerging technology, the science and regulatory requirements can be expected to evolve (see box, "New federal plans to strengthen oversight on biotech foods", p 16). When designing the risk analysis during new product development, this potential for change must be not only recognized but anticipated.

Regulatory involvement in the safety assessments is not a one-time event that happens before commercialization, but one that reaches back into trait discovery, as shown in Figure 1. Discovery research must be conducted under the 1994 National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules. USDA must approve the facilities that conduct the research, which includes inspecting the greenhouses or laboratories where biotech plants are tested.

Before commercialization, the product is field-tested repeatedly by the USDA. If the crop is a pest-protected plant, the EPA joins the oversight process. EPA involvement continues throughout the development process and culminates in approval of the registration for use in commercial agriculture. An FDA food safety assessment must also be completed before any biotech crop product can be commercialized.

**U.S. regulation of biotech crops**

**USDA**

Protects agriculture against invasive genetic modification that may promote the infestation of plant pests or diseases.


**FDA**

Ensures the safety of food and feed products, including those derived from new plant varieties.


**EPA**

Regulates plants and microbes producing pesticidal substances.

New federal plans to strengthen oversight of biotech foods

On May 3, 2000, to clear up some of the unfounded rumors and dispel growing opposition to biotech foods, the Clinton administration unveiled plans to increase federal oversight of genetically modified foods and make details more open to the public. The plans are intended to increase consumer confidence in biotech foods. The Clinton initiative is a result of input received during FDA’s public outreach meetings held late last year and builds on programs already under way at FDA.

The initiatives are broad and sweeping and include three primary components. The most significant component being proposed is for developers of biotech foods and animal feed companies to notify FDA 120 days before marketing a new biotech food or animal feed. Under the new initiative, FDA mandates that specific information (i.e., research results) be submitted to FDA and to the public to help determine whether foods or animal feeds raise issues of potential safety, labeling, or adulteration. FDA plans on posting the results on its Web site. Currently, this process is largely voluntary.

FDA also intends to draft labeling guidelines to assist manufacturers who wish to voluntarily label products containing gene-altered ingredients. To receive maximum consumer input, FDA will develop the guidelines with the use of focus groups and will seek public comment via the World Wide Web. The third change entails USDA becoming involved in validating and certifying new scientific tests for detecting gene-altered ingredients.

In a related step, FDA is planning to augment its food and veterinary medicine advisory committees with scientists who have agricultural biotechnology expertise. The committees will address overarching scientific questions pertaining to biotech foods and animal feeds.

Administration officials stressed that most of the initiatives will be implemented gradually through various rulemaking processes in the upcoming months. However, the critics are not enthusiastic about the changes, because most of them are slated to take place under a new administration that may put less emphasis on the reform measures.

—Marc C. Fitzgerald

Data behind the products

A detailed list of information currently submitted to obtain U.S. registration of biotech crops is shown in the box, “Data submitted to federal agencies for registering U.S. biotech crops.” Specific studies and safety evaluations vary depending on the type of crop. Risk assessment studies for biotech crops can be divided into three broad categories: product characterization, human and animal health, and environmental safety. The most fundamental step, product characterization, provides detailed information about the genetic makeup and design of the biotech crop. This basic information is an integral part of the scientific evaluation of potential risks.

To assess the risk that biotech foods pose to humans, regulatory agencies around the world rely on “substantial equivalence,” which compares biotech foods with their conventional counterparts (9). This approach recognizes that traditional, nonbiotech foods are rarely tested for safety but are accepted as safe when prepared appropriately and used in typical ways based on our long experience of eating them. A finding of substantial equivalence between foods from biotech and conventional crops does not mean that the two foods are identical in every way; rather, it means that the new biotech food item is considered as safe as the traditional food counterpart.

Some critics have claimed that substantial equivalence is merely an excuse for not requiring toxicological testing. In reality, however, this approach requires extensive information about the product and its toxicological or health-related characteristics, such as the presence and level of toxins and the potential for allergenicity. The potential for biotech crops to transfer allergens and thus become a health threat raises some valid concerns. Well before commercialization, extensive comparisons to known allergens are made to identify potential problems. Scientists also continue to develop new testing methods that more effectively and efficiently search for allergens in the human diet, whether they derive from a biotech or a conventionally bred new crop. In addition, the stability of the transgenic protein is determined because easily digested or degraded proteins offer little potential for allergenicity.

Studies to assess ecological and environmental risk evaluate the potential for the crop to adversely affect natural and agricultural ecosystems. Key research areas include the potential to cross-breed with other plants, which could give them a biological advantage as a weedy species; the possibility of the biotech crop itself developing into a problem weed; and the likelihood of the survival of the transgene in the environment. If the crop is a pest-protected plant, the effects on wildlife, including nontarget insects, and the potential to promote insect resistance are also examined.

New approach to risk analysis

At Dow AgroSciences LLC, an analytical-deliberative process for risk analysis is used throughout the life cycle of a product, starting at the early stages of product discovery and proceeding through commercialization. The intent is to meet our own product stewardship demands while addressing regulatory and public concerns.
Data submitted to federal agencies for registering U.S. biotech crops (as of May 2000)

**EPA**
- Product characterization
- Source and function of donor genes and all regulatory sequences
- Description of transformation system
- Characterization of gene product
- Molecular characterization of inserted DNA
- Proposed mode of action
- Equivalency study of microbial test substance to plant-produced protein
- Human health and safety data
- Acute oral toxicity (mice)
- In vitro digestibility (simulated gastric and intestinal fluids)
- Amino acid homology search to known allergens
- Exposure and environmental fate
- Fate in soil
- Quantitative expression of inserted gene products in all tissue types
- Environmental health and safety data
- Dietary effects (honeybee larvae and adults, green lacewing larvae, parasitic wasps, ladybird beetles, catfish or trout, and bobwhite quail)
- Acute toxicity (daphnia, earthworms)
- Supplementary nontarget data
- Efficacy data
- Insect resistance management plan (only for insect resistance traits)
- Herbicide residue study (only for herbicide resistance traits)

**USDA**
- Rationale for development of petitioned crop
- Biology and ecology of recipient crop
- Description of transformation system
- Source and function of donor genes and all regulatory sequences
- Quantitative expression of inserted gene products
- Equivalency study of microbial test substance to plant-produced protein
- Molecular characterization of inserted DNA
- Presence or absence of antibiotic resistance marker genes
- Linkage and segregation analysis, genetic stability
- Agronomic characteristics
- Disease pest resistance characteristics
- Environmental consequences
- Estimated environmental concentration
- Environmental fate in soil
- Nontarget effects
- Weediness
- Recombination (for viral genes)
- Vertical and horizontal transfer of the new genes
- Possible adverse consequences from new cultivar introduction

**FDA**
- Name of crop; applications and uses of food or feed
- Purpose or intended effect of the genetic modification
- Sources and functions of introduced genes
- Expected effect on composition of food or feed
- Identity of introduced genetic material and expressed products
- Composition data (raw agricultural commodity)
- Identities and levels of toxicants
- Allergenicity assessment
- Animal performance study (depends on introduced trait)
- Safety of new or modified substances in the food (e.g., proteins, carbohydrates, fats, or oils)
To satisfy these varied needs, we have adopted a new approach for risk analysis, known as the Orange Book Paradigm (10). The Orange Book Paradigm moves risk characterization from a predominantly science-driven exercise to an analytical-deliberative process in which the concerns of all interested parties are integrated into the risk determination (6). The more emotive or abstract concerns are recognized through continuous dialogue between the developers, the regulatory agencies, and the public (Figure 2). This dialogue can influence the direction of the scientific investigations throughout the process.

In the past, risk assessment was typically a science-driven activity that provided quantitative measures of risk. Although the methodology was rigorous, the assessment was largely separated from the emotive factors that influenced the understanding and perception of risk. This risk analysis process, called the Red Book Paradigm (11), followed a logical, step-wise progression from research to risk assessment, and finally to risk management. Risk analysis under this paradigm did not necessarily exclude consideration of social, economic, and political concerns. These concerns were considered in making and implementing policy, but primarily at the risk management phase and not throughout the entire analysis process.

Today, questions about biotech risks may arise from the most preliminary findings or even from speculation about a hazard. With the speed of modern media coverage, these questions may escalate into full-fledged issues overnight. Also, because biotechnology is an evolving science, continual updating of the specific study requirements to meet regulatory demands can be expected. These forces create a rapidly changing landscape for regulatory requirements and risk analysis. The newer Orange Book Paradigm is much better suited to this new environment, because this approach emphasizes the interaction among scientists and other interested parties to consider all aspects of risk determination and allows a more timely response to new or changing issues.

**Implementation**

Adopting this new holistic approach to understanding and addressing risk may require changes in the traditional structure and scope of risk analysis now used in many industries. Using the new paradigm, risk analysis is not just implemented at the final stages before commercialization, but it must occur throughout the entire life cycle of the product. The goal is not just to develop products that are safe, but also to ensure that their safety is recognized and accepted by the public and regulatory agencies. To achieve these multiple objectives, a company must be closely attuned to the entire spectrum of risk concerns. To develop a successful final product, the producer must listen to, acknowledge, and even anticipate the risk questions that will be raised. Our answers should be based on science and presented in a form that is understandable by the intended audience and that satisfies the concern.

The composition and thinking of the risk analysis team may also need to change. The use of cross-functional scientific teams to analyze risk is fairly standard, but this new paradigm forces teams to reach beyond their typical expertise. Experts in toxicology, ecology, and environmental sciences, as well as in molecular characterization and plant genetics, are critical to risk deliberations for biotech crops. Experts in entomology are needed when dealing with pest-protected plants to address insect resistance management issues. Because the risk analysis will be driven by more than the science, the team composition will need to be broadened beyond the pure scientific disciplines. Experts in regulatory and public affairs must be included to widen the team’s perspective and help recognize not only what questions should be asked based on science but also what other questions will be asked.

**Now and the future**

Contrary to some critics’ claims, biotech crops are tested for composition and safety and are subject to established regulatory reviews before release to the marketplace. Evidence indicates that the system is working, and no evidence exists that foods from biotech crops currently on the market are unsafe. But as with any new technology that promises such a wide range of changes, concerns can be expected to arise. The risk issues challenging biotechnology are not based only on science; many are fueled more by discomfort with technological innovations that bring such change. The questions and concerns of all stakeholders must be heard and acknowledged. The importance of the science has not diminished, but the complexity of the landscape requires the science be approached and used in new ways to address multiple demands.

**Disclaimer**

Approaches and processes described here are used by Dow AgroSciences LLC and do not necessarily represent those used or advocated by other members of the crop protection chemical or biotechnology industries.
References


(9) Food Safety Network. Substantial Equivalence and Its Application in GM Food Safety Assessment; Agri-Food Risk Management and Communication Web Site, University of Guelph; www.oac.uoguelph.ca/riskcomm/plant-agfse-response.htm (accessed May 19, 2000).


George R. Oliver is leader of the Global Exposure and Risk Assessment Group at Dow AgroSciences LLC (9330 Zionsville Rd., Indianapolis, IN 46268; 317-337-4923; goliver@dowagro.com). He leads research efforts involving human, ecological, and environmental risk assessments on a global basis for conventional crop protection chemicals and biotech products. He also has extensive experience in product development for agricultural chemicals and products. He received a B.S. degree in soil science and conservation from North Carolina State University, an M.S. degree in soil science from the University of Illinois, Urbana-Champaign, and a Ph.D. in agronomy from Ohio State University.

James E. Gibson is global leader of the Global Health, Environmental Sciences and Regulatory Group at Dow AgroSciences LLC. He directs scientific and regulatory activities supporting crop protection chemicals and biotech products globally. He has held many advisory positions in professional societies, government, and industry, including president of the Society of Toxicology, secretary-general of the International Union of Toxicology, and member, Board of Scientific Directors of the International Life Science Institute's Risk Science Institute. He received an M.S. degree and a Ph.D. in pharmacology and toxicology from the University of Iowa.

Jeffrey D. Wolt is a risk assessment leader with Dow AgroSciences LLC specializing in biotechnology issues. His current research focuses on risk assessment approaches and methodology for biotech products. He has extensive expertise in chemical bioavailability in the environment and the implications to human and ecosystem health. He received a B.S. degree in bio-agricultural sciences from Colorado State University, an M.S. degree in agronomy, and a Ph.D. in environmental soil chemistry from Auburn University.

Diane M. Shanahan is a regulatory manager at Dow AgroSciences LLC, where she deals with U.S. and global regulation of biotech crops. She has 13 years of experience in the areas of biotech product registration and biotech research and development. She received a B.S. degree in biology from the University of Idaho.

For the Record

In the feature "Eliminating asbestos from fireproofing materials" (Chemical Innovation, June 2000, p 21), we incorrectly listed Jacob Block's academic credentials. He received his B.S. in chemistry from Brooklyn College (CUNY) and his Ph.D. in analytical chemistry from Case Institute of Technology (now Case Western Reserve University, Cleveland, OH).

The biography posted on the Chemical Innovation Web site is correct. Chemical Innovation regrets the error.

—Ed.