The Safety of Foods Developed by Biotechnology

David A. Kessler, Michael R. Taylor, James H. Maryanski, Eric L. Flamm, Linda S. Kahl

By virtue of its broad regulatory jurisdiction over foods, drugs, biologicals, and medical devices, the Food and Drug Administration (FDA) directs its efforts to ensure that safety and other public health issues are properly addressed as the exciting fruits of new biotechnology come to the market. The FDA has already approved human drugs and vaccines, diagnostic devices, and food processing enzymes produced through recombinant DNA techniques and other tools developed by the recent and continuing revolution in the biological sciences.

Recombinant DNA techniques are now being used to develop new plant varieties that will be sources of foods, such as fruits, vegetables, grains, and their by-products. These techniques enable developers to make specific genetic modifications in plants, including modifications that introduce substances into plants that could not be introduced by traditional methods. To ensure the safety of the resulting foods and to foster innovation, the FDA is taking the initiative, before foods from such plants are ready to enter the market, to see that there is an agreed upon scientific basis to evaluate the safety of whole foods and animal feeds derived from new plant varieties. Here, we summarize our regulatory framework and our approach to safety assessment and discuss its scientific basis (*1*).

Our safety assessment approach addresses new varieties of food crops developed by both traditional and newer methods of genetic modification and provides guidance on how safety issues should be addressed. The approach identifies scientific or regulatory issues where developers may need to consult the FDA. In developing this approach, we have examined many techniques now available to plant breeders and the types of food safety issues that might arise as a result of those techniques (*2–7*). However, we focus here primarily on issues associated with foods derived from new plant varieties developed by recombinant DNA techniques. Such foods are now approaching the point of commercial introduction.

We consume in our diet a great diversity of chemical substances. In some cases, these substances are macroconstituents of the daily diet, such as potato starch or wheat gluten. Other substances are microconstituents, such as most flavors, enzymes, vitamins, and minerals. The major classes of food constituents include carbohydrates (mostly monosaccharides, disaccharides, oligosaccharides, and polysaccharides, including gums, starches, and celluloses), fats (mostly triglycerides containing fatty acids of varying chain lengths and degrees of saturation), enzymes and other proteins and peptides, minerals, DNA and RNA, essential oils, waxes, vitamins, pigments, and alkaloids (*2*).

Developers introduce hundreds of new varieties of food plants into commerce every year. Most have improved agronomic characteristics, such as higher yield. Varieties are also being developed with enhanced quality characteristics, such as improved nutritional or processing attributes. To develop new varieties, breeders use all the techniques at their disposal to generate ever more advantageous combinations of genetic traits.

Breeding techniques include hybridizations between plants of the same species, between plants of different species, and between plants of different genera; chemical and physical mutagenesis; interspecies and intergeneric protoplast fusions; somaclonal variation resulting from regeneration of plants from tissue culture; and in vitro gene transfer techniques.

Traditional methods of plant breeding of some major crops have yielded dramatic changes in food composition, including increases in major plant constituents. For example, traditional breeding resulted in the transformation of the kiwifruit from a small berry native to Asia to the recognizable variety in our grocery stores. Hundreds of similar or more subtle improvements in the agronomic, food processing, or other attributes of food crops have been achieved without any significant adverse impact on the safety of foods (*2–4*).

Recombinant DNA techniques, which are being used to achieve the same types of goals as traditional techniques, offer plant breeders a number of useful properties. First, any single-gene trait (and, potentially, multi-gene traits) whose chromosomal location or molecular identity is known can be transferred to another organism irrespective of mating barriers. Second, this transfer can be accomplished without simultaneously introducing undesirable traits that are chromosomally linked to the desirable trait in the donor organism. Thus, the techniques have great power and precision.

Currently, more than 30 different agricultural crops developed with recombinant DNA techniques are being tested in field trials. With these techniques, food crops are being developed to resist pests and disease, to resist adverse weather conditions, to tolerate chemical herbicides, and to have improved characteristics for food processing and nutritional content (Table 1). The genes conferring these traits usually encode proteins that are responsible for the new trait or that directly or indirectly modify carbohydrates or fats in the plant to bring about the desired characteristics. In addition, genes encoding antisense messenger RNA have been introduced to decrease gene expression and thereby bring about the desired new phenotype.

FDA Approach to Regulation

The United States today has a food supply that is as safe as any in the world. Most foods predate the establishment of national food laws, and the safety of these foods has been accepted on the basis of extensive use and experience over many years or even centuries. Foods derived from new plant varieties are not routinely subjected to scientific tests for safety, although there are exceptions. For example, potatoes are generally tested for the glycoalkaloid solanine. The established practices that plant breeders use in selecting and developing new varieties of plants, such as chemical analyses, taste testing, and visual analyses, rely primarily on observations of quality, wholesomeness, and agronomic characteristics. Historically, these practices have been reliable for ensuring food safety (*2–4*).

The Federal Food, Drug, and Cosmetic Act (*8*) gives the FDA authority to ensure the safety of whole foods. This act places a legal duty on those who develop and sell food to assure the safety of the products they offer to consumers and provides the FDA with a range of legal tools to enforce this duty. The FDA can take action to remove a food from commerce if there is even a "reasonable possibility" that a substance added by human intervention might be unsafe [8, section 402(a)(1)]. The FDA also has authority to require formal premar-

D. A. Kessler is Commissioner, Food and Drug Administration (FDA), 5600 Fishers Lane, Rockville, MD 20857; M. R. Taylor is Deputy Commissioner for Policy, FDA; J. H. Maryanski is Biotechnology Coordinator, Center for Food Safety and Applied Nutrition, FDA; E. L. Flamm is in the Office of Biotechnology, FDA; and L. S. Kahl is in the Division of Food and Color Additives, Center for Food Safety and Applied Nutrition, FDA.

ket review and approval of substances intentionally added to food if there is a question about safety (that is, if the substance is not generally recognized as safe or "GRAS") (8, section 409).

Because of the limited nature of most modifications likely to be introduced, the FDA would waste its resources and would not advance public health if it were routinely to conduct formal premarket reviews of all new plant varieties. We will require such reviews before marketing, however, when the nature of the intended change in the food raises a safety question that the FDA must resolve to protect public health. The FDA also has a responsibility to provide scientific guidance on how the safety of foods from new plant varieties should be evaluated, regardless of whether formal FDA review and approval are required.

Safety Assessment: Scientific Basis

Our safety assessment approach (Fig. 1), like that of others (2–6) addresses important food safety issues that pertain to the host plant, donor organisms, and new substances that have been introduced into the food. The host plant is a benchmark for considering modifications that may affect the safety of food derived from new varieties. Potential new substances considered in this safety assessment are proteins, carbohydrates, and fats and oils because these are the substances that will be introduced or modified in the first plant varieties developed by recombinant DNA techniques.

The host plant. The host is the plant that is genetically modified and is the recipient of any newly introduced traits. In general, it is a species commonly used as a source of food. We expect that developers will consider information consistent with currently accepted scientific practices, such as the potential adverse effects of an altered metabolic pathway in the plant, the inheritance of the introduced genetic material as a single Mendelian trait, and the genetic stability of the new plant variety. In principle, factors that favor stability and facilitate subsequent genetic manipulation include a minimum number of copies of the introduced genetic material and a single site of insertion. How critical these factors are for maintaining stability is unclear because virtually all plants have multi-gene families.

Developers should consider changes in the concentrations or bioavailability of important nutrients for which a food is widely consumed. For example, if a new tomato variety contained no vitamin C, consumers would need to be informed of that fact through appropriate labeling (for example, a change in the common name).

Most plants produce a number of toxicants and antinutritional factors, such as protease inhibitors, hemolytic agents, and neurotoxins, presumably as a means of resisting natural predators. The concentrations of toxicants in most species of domesticated food plants (for example, corn and wheat) are so low as to present no health concern. In others (for example, potato and rapeseed), breeders routinely screen new varieties to ensure that toxicant concentrations are within an acceptable range. In some cases (for example, cassava and kidney bean), proper preparation, such as soaking and cooking, is required to produce food that is safe to eat (2–4).

Additionally, plants, like other organisms, have metabolic pathways that no longer function because of mutations that occurred during evolution. Products or intermediates of some of these pathways may include toxicants. In rare cases, such silent pathways may be activated by the introduction or rearrangement of regulatory elements, or by the inactivation of repressor genes by point mutations, insertional mutations, or chromosomal rearrangements. Similarly, toxicants ordinarily produced at low concentrations in a plant may be produced at higher levels in a new variety as a result of such occurrences.

However, the likelihood of such events occurring in food plants with a long history of safe use is low. The potential of plant breeding to activate or upregulate pathways synthesizing toxicants has been effectively managed by sound agricultural practices, as evidenced by the fact that varieties with unacceptably high levels of toxicants have rarely been marketed (2–4).

Therefore, the toxicants that are of concern in any particular species are those that have been found at unsafe concentrations in some lines or varieties of that species or related species. In many cases, characteristic properties (such as a bitter taste associated with alkaloids) are known to accompany elevated concentrations of specific natural toxicants, and the absence of bitter taste may provide an assurance that these

Table 1. Examples of food crops under development.

Trait	Genetic modification	Examples of food crops with the trait
Herbicide tolerance		
Glyphosate tolerance	5′-enolpyruvylshikimate-3′-phosphate synthase	Tomato, cotton, soybean, corn, rapeseed
Sulfonylurea/chlorsulfuron tolerance	Acetolactate synthase	Tomato, cotton
Glufosinate/bialophos tolerance	Phosphinothricin acetyltransferase	Corn, soybean, tomato, alfalfa, rapeseed
Bromoxynil tolerance	Nitrilase from *Klebsiella ozaenae*	Cotton, potato
2,4-dichlorophenoxy acetic acid tolerance	*Alcaligenes eutrophus*/2,4-*D* monooxygenase	Potato
Disease/pest resistance		
Resistance to lepidopteran insects	*Bacillus thuringiensis* delta endotoxin	Tomato, cotton, corn, rapeseed, rice, potato, apple, walnut
Resistance to viruses	Various viral coat proteins	Cantaloupe, squash, tomato, corn, potato, alfalfa
Resistance to bacteria	Cecropin	Potato
Resistance to European corn borer	Wheat germ agglutinin	Corn
Resistance to *Rhizoctonia solani*	Chitinase	Potato
Other agronomic properties		
Cold tolerance	Fish "antifreeze protein"	Tomato
Stress tolerance	Stress-alleviating enzymes	Potato
Altered ripening	Polygalacturonase antisense gene	Tomato
Post-harvest properties		
Simple sugar increase	Metabolic enzymes	Potato
Starch increase	Metabolic enzymes	Potato
Altered fatty acid content	Antisense desaturase and thioesterase oil modification genes	Rapeseed
Increased solids or dry matter content	Pectin methylesterase antisense gene; metabolic enzymes	Tomato, potato
Altered amino acid content	Seed storage proteins	Corn, soybean, rice, sunflower

Source: *Federal Register* notices published by the Division of Biotechnology, Biologics, and Environmental Protection, Animal and Plant Health Inspection Service, U.S. Department of Agriculture.

toxicants have not been elevated to unsafe levels; in other cases, analytical or toxicological tests may be necessary.

The donor. The donor (plant, microorganism, or animal) is the source of the new trait. We expect that producers will consider information consistent with currently accepted scientific practices that might relate to the presence of unintended toxicants, such as history and derivation of molecular constructs (for example, passage through microbial hosts), known activities of any introduced regulatory sequences (for example, environmental, developmental, and tissue-specific effects on promoter activity), and the potential for inadvertently introducing undesirable substances (for example, due to the expression of extraneous open reading frames).

Toxicants known to exist in the donor, related species, or progenitor lines may be transferred to the new plant variety, for example, during hybridization of a cultivated variety with a wild, poisonous relative. The possibility that donor-derived toxicants could occur in food derived from a genetically modified plant should be considered.

One of the questions raised most frequently about the use of recombinant DNA techniques to develop improved food crops concerns the safety for consumption of substances (now primarily proteins, carbohydrates, and fats and oils) that will be introduced into foods such as fruits, vegetables, grains, and their by-products. Here we discuss the scientific issues pertaining to these substances in food derived from the new plant variety.

Proteins. Proteins (including antisense modifications that modulate expression of native proteins) make up the largest group of substances being introduced into food through recombinant DNA techniques. Our approach in evaluating uncertainty associated with proteins is first to ask, "Does the protein have a safe history of use in food, or is it substantially similar to such a food component?" The scientific issues pertaining to proteins that are derived from other food sources, or that are substantially similar to proteins that are derived from food sources, are known toxicity, allergenicity, and dietary exposure.

Thousands of proteins have been safely consumed in the human diet. In fact, the eukaryotic cell contains 5000 or more different polypeptides. Genetic polymorphism, the occurrence of more than one allele of a gene, also contributes to the diversity of proteins in the diet. For example, six alleles of beta-galactosidase have been identified in 39 widely used inbred lines of corn (9). Variation may also occur as a result of posttranslational processing (for example, glycosylation or methylation pattern of the host plant).

This variation is also seen in enzymes derived from microorganisms used in food processing. Enzymes that have the same fundamental catalytic activity may differ in DNA sequence, protein structure, and functional properties (*10*). For example, alpha-amylases from different organisms may differ in optimal conditions of use, such as temperature and pH, and substrate affinity.

Generally, enzymes that are substantially similar to enzymes known to be safely consumed (including minor variations in structure or function) would not raise safety concerns (*5, 6, 11*). For example, in food crops a gene coding for an enzyme whose catalytic activity confers herbicide resistance may be isolated from a plant or bacterium, subjected to site-directed mutagenesis to enhance its herbicide resistance, and introduced into the desired host plant to substitute for the biochemical activity of the plant enzyme that is sensitive to the herbicide. However, some enzymes produce toxic substances (for example, the enzymes that convert cyanogenic glycosides to cyanide) that would raise safety questions.

As discussed above, a variety of proteins are present in the diet and have a history of safe consumption. In general, proteins that are currently consumed or substantially similar to proteins already in the diet do not pose specific safety concerns. A seed storage protein, for example, may be transferred from one plant species to another to improve nutritional quality. However, a number of groups of proteins present in common food sources are known to be toxic or antinutritional (for example, lectins and protease inhibitors). Because processing (such as soaking or cooking) may reduce or eliminate the toxic effects of these proteins, many foods that contain these toxic substances are poisonous if eaten raw but safe when properly prepared. Sound scientific practices dictate that such toxic proteins not be introduced into food or animal feed components of new plant varieties.

Many foods produce an allergenic response in some individuals. Foods that

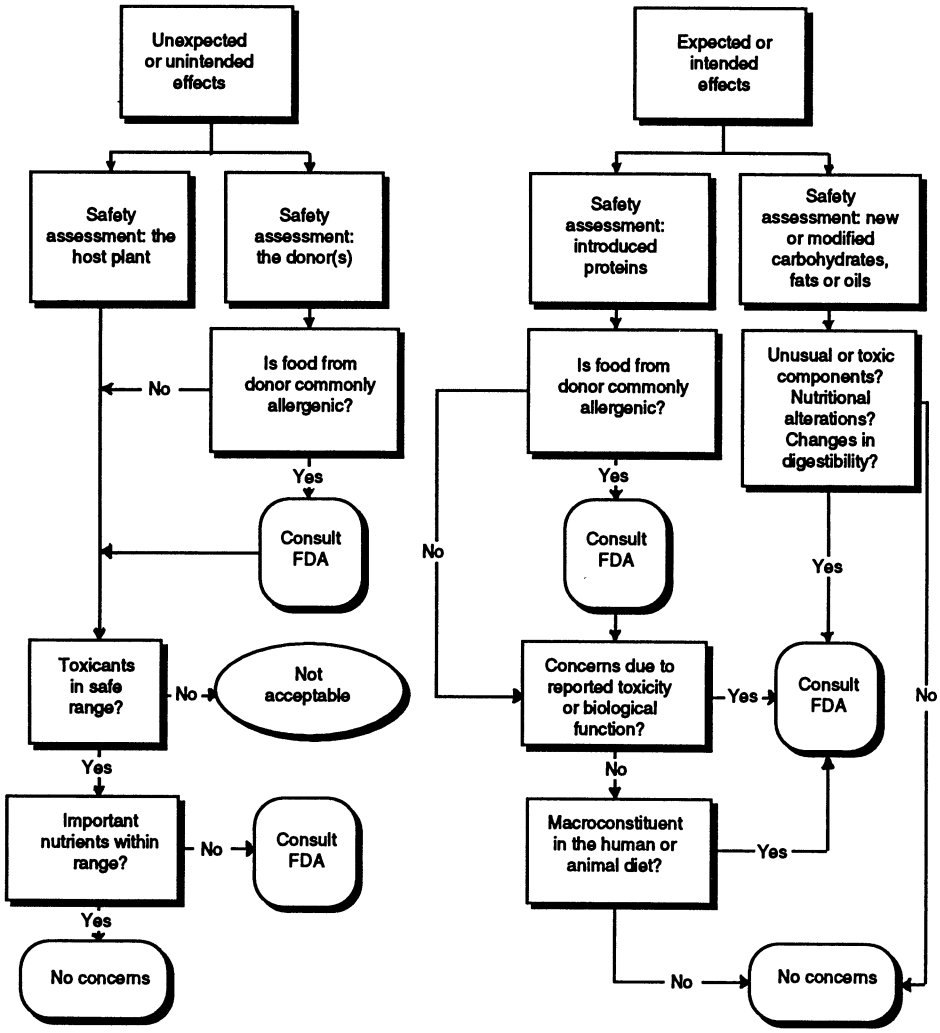

Fig. 1. Summary of safety assessment of new varieties.

(*Continued on page 1832*)

(*Continued from page 1749*)

commonly cause allergenic responses include milk, eggs, fish, crustacea, mollusks, tree nuts, wheat, and legumes. Although only a small fraction of the thousands of proteins in the diet have been found to be allergenic, all known food allergens are proteins. The transfer of proteins from one food source to another might therefore confer on food from the host plant the allergenic properties of food from the donor plant. For example, the introduction of a peanut allergen into corn might make that variety of corn newly allergenic to people ordinarily allergic to peanuts.

In some of these foods, the protein responsible for the allergenicity is known (for example, gluten protein in wheat). In such cases, the precision of methods such as recombinant DNA techniques allows the developer to determine whether the allergenic determinant has been transferred from the donor to the new variety. In many foods, however, the protein responsible for the allergenicity is not known. In these cases, well-designed in vitro tests, such as serological tests, may provide evidence that the suspected allergen was not transferred or is not allergenic in the new variety.

A separate issue is whether any new protein in food has the potential to be allergenic to a segment of the population. At this time, we are unaware of any practical method to predict or assess the potential for new proteins to induce allergenicity.

Uncertainty may exist about the safety for consumption of a protein that has not been a constituent of food previously (or has no counterpart in food that would serve as a basis for comparison of safety). The degree of testing these new proteins should be commensurate with any safety concern raised by the objective characteristics of the protein.

Generally, the function of proteins that have been introduced into food by recombinant DNA techniques is well known, and these proteins are not known to exert toxic effects in vertebrates. If such well-characterized proteins do not exhibit unusual functions, safety testing will generally not be necessary.

However, certain groups of proteins are known to be toxic to vertebrates. These include bacterial and animal toxins, hemagglutinins, enzyme inhibitors, vitamin-binding proteins (avidin), vitamin-destroying proteins, enzymes that release toxic compounds, and selenium-containing proteins (*12*). For such substances, testing may be the only means available to ensure safety.

Carbohydrates. Developments that affect carbohydrates will often be modifications of food starches, presumably affecting the content of amylose and amylopectin, as well as the branching of amylopectin. Such modified starches are likely to be functionally and physiologically equivalent to starches commonly found in food and thus would not suggest any specific safety concerns. However, if a vegetable or fruit is modified to produce high concentrations of an indigestible carbohydrate that normally occurs at low concentrations or to convert a normally digestible carbohydrate to an indigestible form, nutritional questions may arise.

Fats and oils. Some alterations in the composition or structure of fats and oils, such as an alteration in the ratio of saturated to unsaturated fatty acids, may have significant nutritional consequences or result in marked changes in digestibility. Such changes may warrant labeling that describes the new composition of the substance. Additionally, safety questions may arise as a result of the presence of fatty acids with chain lengths greater than C_{22}, fatty acids with cyclic substituents, fatty acids with functional groups not normally present in dietary fats and oils, and fatty acids of known toxicity, such as erucic acid.

Nonclinical Safety Testing

Animal feeding trials of foods derived from new plant varieties are not conducted routinely. However, in some cases testing may be needed to ensure safety. For example, substances with unusual functions or that will be new macroconstituents of the diet may raise sufficient concern to warrant testing. Tests could include metabolic, toxicological, or digestibility studies, depending on the circumstances.

Developers may also need to conduct tests on the "wholesomeness" of foods derived from new plant varieties as a means of ensuring that the food does not contain high levels of unexpected, acutely toxic substances. Such tests may provide additional assurance to consumers that food developed by new technology is as safe as food derived from varieties already in their grocery stores. However, animal tests on whole foods, which are complex mixtures, present problems that are not associated with traditional animal toxicology tests designed to assess the safety of single chemicals. Potential toxicants are likely to occur at very low concentrations in the whole food, and the tests may therefore be inadequately sensitive to detect toxicants. Efforts to increase the amount of whole food ingested by the test animals in order to increase the sensitivity and attempt to establish a traditional margin of safety (for example, a 100-fold safety factor) may not always be possible. When tests are contemplated, careful attention should be paid to test protocol, taking into account issues such as nutritional balance and sensitivity.

FDA's science-based approach for ensuring the safety of foods from new plant varieties focuses safety evaluations on the objective characteristics of the food: The safety of any newly introduced substances and any unintended increased concentrations of toxicants beyond the range known to be safe in food or alterations of important nutrients that may occur as a result of genetic modification. Substances that have a safe history of use in food and substances that are substantially similar to such substances generally would not require extensive premarket safety testing. Substances that raise safety concerns would be subjected to closer inquiry. This approach is both scientifically and legally sound and should be adequate to fully protect public health while not inhibiting innovation.

REFERENCES AND NOTES

1. For a full discussion see FDA's *Statement of Policy: Foods Derived from New Plant Varieties, Fed. Regist.* **57**, 22984 (29 May 1992).
2. International Food Biotechnology Council, *Regul. Toxicol. Pharmacol.* **12** (no. 3) (1990), part 2.
3. Nordic Council of Ministers and The Nordic Council, *Food and New Biotechnology* (Scantryk, Copenhagen, 1991).
4. *Approaches to Assessing the Safety of Crops Developed Through Wide-Cross Hybridization Techniques*, proceedings of a Food Directorate Symposium held 22 November 1989, Ottawa, Canada (Food Directorate, Health Protection Branch, Health and Welfare Canada, Ottawa, 1990).
5. "Strategies for assessing the safety of foods produced by biotechnology" (World Health Organization, Geneva, 1991).
6. "Report on Food Safety and Biotechnology" (Group of National Experts on Safety in Biotechnology, Organization for Economic Cooperation and Development, Paris, in press).
7. D. D. Hopkins, R. J. Goldburg, S. A. Hirsch, "A Mutable Feast: Assuring Food Safety in the Era of Genetic Engineering" (Environmental Defense Fund, New York, 1991).
8. 21 U.S.C. §321 *et seq.*
9. D. B. Berkowitz, *Biotechnology* **8**, 819 (1990).
10. M. Vihinen and P. Mantsala, *Crit. Rev. Biochem. Mol. Biol.* **24**, 329 (1989).
11. M. W. Pariza and E. M. Foster, *J. Food Prot.* **46**, 453 (1983).
12. W. G. Jaffe, in *Toxicants Occurring Naturally in Foods* (National Academy of Sciences, Washington, DC, 1973), pp. 106–128.