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LABELING OF FOOD-PLANT BIOTECHNOLOGY PRODUCTS

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Introduction

The U.S. Food and Drug Administration (FDA) (1992, 1993) proposed and requested comments about a policy for labeling of human and animal foods derived from new plant varieties. These policy guidelines affirm the suitability of current regulations for overseeing the safety, wholesomeness, and labeling of both traditionally produced and genetically engineered food plants. A review of the scientific evidence by a Council for Agricultural Science and Technology task force indicates that the proposed approach is well reasoned. It provides an appropriate means of regulating the foods derived from new plant products according to laws regarding safety and labeling of foods and ingredients. Labeling requirements should depend on safety and nutritional characteristics, not on development method. Before reaching this conclusion, the task force addressed ten fundamental questions.

What Is Genetic Engineering?

In this report, *genetic engineering* (often referred to as *biotechnology*) is defined as the manipulation of genetic information by means of techniques other than those classically employed in standard breeding technologies under natural conditions. Thus, according to this definition, genetic engineering includes materials derived through genetic transformation and recombinant deoxyribonucleic acid (rDNA) technology.

What Is the Impact of Genetic Modification on Quality, Volume, Nutritional Value, and Cost of Food Plants?

For hundreds of years, plant breeders have used genetic material from many sources to improve food crops. These breeding procedures have provided consumers with choices from an expanded variety of foods with improved quality and nutritional content at decreased cost. For example, plant breeding has transformed inedible wild tomatoes into disease-resistant edible varieties ranging from cherry tomatoes to large, bright-red salad tomatoes. It has given consumers the choice between large yellow or white ears of hybrid corn with kernels in ordered rows and small multicolored ears of native maize (*Zea mays* L.) with irregularly ordered kernels. Genetic enhancement of tree crops has resulted in new and improved orchard varieties.

The development of plants with improved disease resistance and production vigor has enabled one U.S. farmer to produce enough food for approximately 120 people. Plant breeding, together with improved agricultural practices and processing techniques, has lowered food costs in the United States so that only about $.09 from each consumer dollar is devoted to food and beverage purchases (Putnam and Allshouse, 1992). In contrast, food and beverage purchases exceed 20% of personal consumption expenditures in most countries (Putnam and Allshouse, 1992). Genetic engineering techniques widen the source of genes for crop improvement and provide more precise methods by which to alter plant genetic material (Gasser and Fraley, 1989; Goodman et al., 1987). The resulting improvements can further increase the quality, volume, and nutritional value of food crops available to consumers; improve environmental safety; and decrease animal and human food costs.

Consumers today choose products from many fruits, vegetables, and grains that have been bred for desirable traits. Photograph by Peter Krumhardt, Madrid, Iowa.

How Do Traditional Plant Breeding and New Genetic Biotechnology Techniques Compare?

Until the 1980s, plant breeders used only traditional approaches to transfer desired genes into crops. For example, a plant containing a majority of desired characteristics might be improved by being crossed with another plant carrying a gene for disease resistance. Both plants, however, contain tens of thousands of genes, and the process of mixing and sorting them during classical breeding is random, imprecise, and uncontrollable. Progeny of the cross would be examined in the field and repeatedly selfed or back-crossed, and offspring containing the majority of desirable traits would be identified. Identification of desirable progeny carrying the disease resistance gene would rely heavily on selection schemes and often would require 7 to 12 generations, or selection cycles, to achieve desired results. Similar processes could follow in vitro fertilization and embryo rescue techniques if necessary to achieve wide hybridizations normally unsuccessful by traditional sexual crosses.

In contrast, crop improvement through genetic engineering involves more efficient gene transfer than does standard sexual crossing. When optimized, genetic engineering (including rDNA technology) makes it possible, without carrying in undesirable genes, to introduce new genes from more sources. Thus, crops may be improved more rapidly than when classical plant-breeding strategies are used. As with traditional breeding strategies, gene transfer through engineering techniques may inactivate host genes or have other unforeseen effects on host characteristics. For this reason, all genetically engineered plants must be analyzed by plant breeders and agronomists as thoroughly as are plants developed by classical methodologies.

The application of genetic engineering techniques is, in part, a refinement of traditional plant genetics and breeding practices (American Medical Association Council on Scientific Affairs, 1991). New genetic technologies improve the precision with which plant genetic material is altered and most often produce phenotypes (observable characteristics) identical to those derived through traditional techniques. For example, a long-keeping tomato that stays firm for many weeks under controlled storage conditions has been bred traditionally. Fresh-market tomatoes have been improved similarly by rDNA techniques, including by transfer of DNA between different tomato cultivars or different types of organisms. Because genetic engineering permits the breeder to transfer novel genes that cannot be developed by traditional breeding methods, it will be important to address food safety issues of such tomatoes (and other crops) to ensure consumer confidence.

Does Product or Process Determine Food Safety?

Traditional plant breeding has produced plant cultivars containing genetic information from widely different sources. Crossing two related wild-plant species results in a mixture of genetic information that ultimately may lead to agronomically desirable crop products. Some crosses have introduced genes previously absent from cultivated varieties.

Embryo rescue and irradiation breeding also have played important roles in plant-breeding processes. By chromosomal breakage, rearrangement, or other genetic disruption, irradiation most likely has deactivated, or eliminated, genes and thereby helped create plant cultivars with desirable traits. Careful analysis of agronomic properties and quality characteristics and a long history of safe consumption of products produced by these means have led to acceptance by consumers and by the food industry.

The FDA (1992) has proposed that the safety of plant foods developed by means of genetic engineering techniques be reviewed under current regulations for plant varieties produced by traditional means. The guidelines are applicable to all new plant varieties, regardless of development method. Linking safety issues to the product and not to the process is most appropriate.

Key nutrition and safety issues relate to the end product, whether derived by traditional breeding techniques or genetic engineering. Concerns focus on whether the new variety is materially different from the parental variety and whether the introduction of new traits poses safety questions beyond those posed by the parental variety. Thus, both current and future assessments of new varieties should focus on (1) the characteristic toxicants of host plant and donor species; (2) the possibility of food allergens being transferred from one food source to another; (3) the composition and availability of nutrients; (4) the safety and nutritional value of introduced proteins; and (5) the identity, composition, and nutrient content of modified food components, specifically of carbohydrates, fats, and oils.

Except for its unique potential to introduce new antigens, genetic engineering has little more potential for negative impact on the quality or the safety of a food or an ingredient than do traditional technologies. And genetic engineering, specifically rDNA technology, can introduce one or several genes with greater precision than can other genetic modification techniques. Consequently, establishment of the safety of a material must be based on the product of modification and not on the process.

What Determines the FDA's Role in Regulation?

The FDA has primary responsibility for ensuring the safety of commercial foods and food additives and works closely with other federal agencies that have food related responsibilities. Its partners include both the Animal and Plant Health Inspection Service (APHIS) of the U.S. Department of Agriculture (USDA), which regulates meat and poultry products, and the U.S. Environmental Protection Agency (EPA), which regulates certain pesticidal applications and field crop properties. The authority of the FDA to ensure the safety of whole foods is defined by section 402(a)(1) of the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, and the implementing regulations in Title 21 of the Code of Federal Regulations. The Food Additives Amendment (enacted in 1958) provides for a science based standard requiring producers and processors to demonstrate the safety of food additives to the FDA. These laws also provide the FDA with full authority to regulate foods originating from genetically engineered plants.

What Is the Current Experience in Field Testing and Evaluating Genetically Modified Crop Plants?

Transgenic plants have been modified to contain additional genetic information. Since 1986, more than 1,000 field tests with transgenic plants have been conducted by scientists within the public and private sectors at locations around the world (Beck and Ulrich, 1993; Fox, 1994; Gasser and Fraley, 1989). In the United States, the APHIS has primary responsibility for oversight of field testing genetically engineered crop plants and shares jurisdiction with the EPA for plants with certain pesticidal properties. The first field studies were designed to compare the growth and development of transgenic plants containing a marker gene with the

growth and development of nontransgenic plants. As expected, transgenic plants performed in much the same manner as did nontransgenic plants. More extensive tests subsequently were conducted to evaluate the efficacy of the introduced gene to confer the desired trait. United States field test regulations have been modified to reflect acquired experience.

Field tests have involved transgenic tomato, potato, oil-seed rape, soybean, cucumber, squash, papaya, maize, cotton, and rice plants evaluated for pest and herbicide resistance, delayed fruit ripening, and modified solids content. Although the results of several field tests have been published in peer reviewed journals, many others probably will be published only as seed trade literature at marketing time.

Field trials published to date generally have been successful. In these trials, plants have been evaluated for single or multiple traits. Based on field trial results, companies hope to choose products that have commercial value, e.g., tomato fruits that soften slowly after being picked at a near-ripe stage, cotton plants that resist insect damage, potato plants that resist attack by the Colorado potato beetle and multiple viral diseases, squash plants that resist viral diseases, and soybeans that tolerate the environmentally friendly herbicide glyphosate.

Equally essential to the widespread application of agricultural biotechnology is the fact that there have been no dramatic surprises in field tests. For example, no evidence exists that tested plants represent a risk to the environment or to the people involved in testing. More importantly, members of the regulatory community are gaining increased confidence in the use of transgenic plants, in terms of both plant health and environmental safety. But evidence of field performance, no matter how compelling, may fail to reassure the public about food safety issues.

How Is Safety, or GRAS Status, of Certain Crops and Foods Determined?

Most plant foods were being consumed by humans well before the institution of state and federal food regulations. The safety of these foods has been accepted as a result of decades and even centuries of use and experience. Due to their long history of safe use, these foods are *generally recognized as safe* (GRAS). Hundreds of new plant varieties are introduced to the market annually but only after extensive testing for 10 to 100 site-years or for 5 to 10 years by the plant breeder (U.S. Food and Drug Administration, 1992). During testing, well established practices are used to evaluate agronomic characteristics such as growth performance, stress resistance, pest susceptibility, seed production, phenotypic stability, and environmental effects; and quality characteristics such as wholesomeness, nutrient content, texture, flavor, appearance, and processing suitability. During the evaluation process, plants with undesirable traits are eliminated.

These well-established testing procedures have a history of reliability in ensuring food and feed safety. As a result, foods derived from new varieties produced by traditional crosses between GRAS species are not subjected routinely to FDA safety review before marketing (U.S. Food and Drug Administration, 1992). Exceptions include new potato varieties tested for the alkaloid solanine, new oil rape varieties tested for erucic acid, and other new varieties derived from parents containing natural toxicants.

What Measures Are Proposed for Continued Evaluation and Safety of New Crops Developed by Means of Biotechnology?

Key issues important in assessing the safety of human and animal foods derived from new plant varieties are (1) whether the new variety is materially different from the parental varieties and (2) whether the introduction of new traits poses safety questions beyond those posed by the parental varieties (International Food Biotechnology Council, 1990; Kessler et al., 1992; U.S. Food and Drug Administration, 1992; World Health Organization, 1991, 1993). An appropriate mix of genetic, compositional, and toxicological information about the host plant, the introduced trait, and the food product is essential (International Food Biotechnology Council, 1990).

Crops improved by genetic engineering, or bio-

technology, will and should be subjected to the same extensive testing as are traditionally bred plants. In assessing the safety of human and animal foods derived from new plant varieties, the FDA's proposed policy (Kessler et al., 1992; U.S. Food and Drug Administration, 1992) addresses safety issues pertaining to the host plant being modified genetically, the donor organism serving as the source of a new trait, and the substances being introduced. The proposed policy recommends, and the biotechnology community (International Food Biotechnology Council, 1990) has considerable favorable experience with, a decision-tree approach to evaluating transgenic crop safety.

As for products of traditionally bred plants, safety evaluations of new, genetically modified plant products will continue to be based on comparisons with the nutrient composition and toxicants present in the traditionally bred counterpart (International Food Biotechnology Council, 1990; Kessler et al., 1992; U.S. Food and Drug Administration, 1992). These comparisons, as well as data describing genetic changes and exposure assessments, constitute the basis for rigorous safety evaluations.

Labeling plant-food products to supply information about safety is both appropriate and necessary. The potential exists for all plant breeding techniques to create unexpected effects or to increase production of known toxic substances. The probability that plant breeding will result in a safety hazard, however, is minimized by currently mandated testing because well-established practices described in the previous section have allowed plant breeders to identify and to eliminate plants with adverse traits.

Plants have been modified to reduce naturally occurring toxicants. Industrial oilseed rape, for example, yields an inedible oil containing toxic levels of erucic acid and glucosinolates. Plant breeders have used traditional breeding methods to produce a variety of rape yielding an edible oil containing less than 2% erucic acid and considered GRAS for food use. Varieties containing more toxicants than do parental varieties are being and will continue to be eliminated. Assays for toxicants are being and should continue to be conducted regardless of production method.

Of major concern to most scientists, regulators, and potential consumers is the possibility that rDNA breeding techniques will introduce new allergens into foods. If a trait is transferred from a source known to cause allergy, e.g., milk, eggs, or peanuts, the possible allergenicity of the new product clearly must be assessed. Safety assessments of such a food may include qualitative and quantitative determinations of introduced proteins, information about the origin of the proteins, any known or suspected allergenicity, evidence of consumption of the proteins in other foods at similar levels and under similar processing conditions, biological function, chemical differences from and similarities to edible proteins, and presence of host-specific translational modifications (U.S. Food and Drug Administration, 1992). If the new biotechnologically derived product is allergenic, labeling is appropriate and will be required. Currently, however, assessing potential allergenicity of gene products from plants not associated with known food sensitivities remains problematic. To solicit input about this issue, the FDA, the EPA, the USDA, and the National Institutes of Health jointly sponsored a workshop on allergenicity in April 1994. The FDA is developing policy concerning food allergenicity.

Labeling also is desirable under other circumstances. For example, the level or availability of nutrients in plants may be altered as a result of breeding methods. New plant varieties retaining most of the characteristics of the parental varieties retain the parental name. However, when a new plant variety, whether developed by classical methods or by genetic modifica-

The DNA double helix is the genetic information of nearly all living organisms. The parallel strands are connected by matching base pairs of ribose sugar molecules: adenine (A) and thymine (T); guanine (G) and cytosine (C). A segment of DNA, a *gene*, serves as a blueprint for a protein.

tion through biotechnology, differs significantly from its parents, labeling is appropriate.

Assessments of the safety of components introduced into foods through genetic engineering are ongoing and should be continued. The rigor of these assessments should depend on the source and the nature of the gene transferred. For example, a gene coding for the neomycin phosphotransferase II (NPTII) protein often is used as a selectable marker in generating transgenic plants. Use of the marker introduces a protein not normally found in foods.

In a recent study (Fuchs et al., 1993a), a microbial host was used to produce large quantities of the NPTII protein from the NPTII plant marker gene. The NPTII proteins from microbial and transgenic plant sources were purified and compared. The two proteins had comparable molecular weights, amino-terminal amino acid sequences, and biological activities; both lacked attached sugars. They reacted similarly to antibodies and had comparable epitope structures (Fuchs et al., 1993a). These evaluations revealed that the plant and the microbial NPTII proteins were chemically and functionally equivalent.

The digestive fate of the NPTII protein also was assessed (Fuchs et al., 1993b). The microbially produced NPTII protein was digested rapidly under simulated mammalian digestive conditions. Large doses of the microbial NPTII protein were fed to mice. Administration of a millionfold greater dose of the NPTII protein to mice than the average daily amount consumed in a normal diet caused no adverse effects (Fuchs et al., 1993b). These results demonstrated that, like other dietary proteins, the NPTII protein is digested rapidly and is nontoxic to mammals (Fuchs et al., 1993b). These data, along with data from other reports (Calgene, Inc., 1990, 1993; Flavell et al., 1992; Nap et al., 1992), provide evidence for the safe application of the NPTII marker to plant foods.

Bacterial plasmids are used to introduce genes with desired traits, such as resistance to a virus, into plant chromosomes.

How Would Segregating Genetically Engineered Foods and Ingredients Through the Food-Distribution Chain Affect Food Supply and Cost?

Complex problems would be encountered if labeling were required for all foods modified by genetic engineering. A mandate for labeling such foods would require that different plant varieties be segregated from the time they enter the food chain—usually as seeds planted on farms across the country—through processing and into the retail food market. The task of segregating and labeling foods containing ingredients from genetically engineered crops would be extremely difficult if not impossible. For example, the agronomic characteristics of varieties of traditionally bred wheat grown in one state may differ substantially from those of varieties grown in other parts of the country. One variety may be drought resistant; another, cold hardy. Yet all varieties may be blended for processing into numerous products, including cereals, pastas, cake mixes, breads, and food coatings.

Although engineering a wheat variety for disease resistance would reduce the need for pesticides and reap significant environmental and cost benefits, segregating the variety throughout the food chain could not be accomplished without increasing costs and thus probably would not happen. Mandatory generic labeling of all

products of biotechnology without regard for health and safety concerns would block adoption of environmentally friendly, economical production techniques that would benefit society substantially.

In most instances, there will be no available tests to distinguish between foods derived from transgenic and nontransgenic crops. Traits introduced by means of genetic engineering may be identical to those that could be introduced by traditional breeding and selection. Genes introduced by rDNA technology will be disseminated upon further crop breeding. Therefore, for mandatory labeling to be applied appropriately, new generations would have to be monitored for the trait unless new seed were purchased each year. The lack of analytical methods for identifying genetically engineered foods would make enforcement of mandatory labeling problematic.

Niche markets commanding premium prices probably exist for nongenetically engineered crops. It certainly would be more practical to label genetically engineered produce than processed foods. But to the authors' knowledge, no risk-benefit analyses of the cost of mandatory labeling of genetically modified foods have been conducted. Is it fair, in the absence of safety concerns, to require everyone to pay the inevitable increase in food costs that would result from mandatory labeling?

How Can Labeling Be Most Useful?

The purpose of labeling is to provide consumers with the information that they desire about the foods that they eat. This obligation is taken seriously by food companies, which answer thousands of calls weekly about food issues and distribute educational information through supermarkets, restaurants, and the media. Product labels can neither possibly nor practically answer every consumer question. Labeling should be based primarily on safety concerns and secondarily on product identity. In the absence of a significant hazard and if the newly engineered plant conforms to the identity of the parental plant, no further action is required. If the plant is substantially different, a new identity should be given for labeling purposes. Thus, labeling information should be reserved for critical health and safety information at the point of purchase.

Conclusions

The FDA is responsible for ensuring the safety of all foods, whether they are produced by means of traditional breeding, genetic engineering, or combined techniques. Determining the safety and the wholesomeness of a new plant product by evaluating its characteristics and not its means of development is logical and makes consumer safety a first priority. At this writing, federal guidelines do not require labeling for foods simply because they are derived from new plant varieties.

The usefulness of labeling foods as genetically engineered may be questioned for several reasons. First, such a label would provide no information about the safety or the composition of new plant cultivars. Second, such labeling could suggest to consumers that the food is less safe than or is materially different from unlabeled food. Third, segregation of products from production through processing to the marketplace, where possible, would reduce end user discretion. And fourth, all end users inevitably would pay increased food costs.

Genetic engineering is one of many tools enabling plant scientists to improve the standard of living in the United States and throughout the world. Possible contributions include increased food production through increased resistance to drought, salinity, and heat or cold; increased disease and pest control; increased yields; improved efficiency of feed and fertilizer utilization; and optimization of nutrients in human and animal foods. Assured safety is essential for all foods regardless of development method. Clearly, discussions about the role of labeling in ensuring food safety should continue.

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