Biotechnology at the Dinner Table: FDA's Oversight of Transgenic Food

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ABSTRACT: The U.S. Food and Drug Administration (FDA), which has statutory authority for protecting the safety and quality of the food supply, provides the oversight for genetically modified foods cultivated and marketed within the American agricultural system. This article examines the FDA's policies on genetically modified foods including its voluntary consultation program and its proposed rule on premarket notification and data submission. The FDA's consultations of foods modified for delayed ripening and herbicide tolerance are reviewed. The article also discusses the FDA's science-based approach for evaluating whether there are any potential adverse health effects of genetically modified food products. The agency has chosen an approach to risk assessment that takes account of both product characteristics and the process through which the food is developed.

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A world economy with capital, goods, and credit flowing across seamless trading networks, referred to as globalization, has been the brainchild of Western industrial nations. One of the first tests of economic globalization has been the introduction of agricultural biotechnology—a sector developing new food crops through genetic engineering. The United States has been a leader in the production of genetically modified (GM) crops. But many European countries that are members of the World Trade Organization, the international group that monitors and mediates violations of free trade, have been highly skeptical of the safety of GM crops. The result has been a transatlantic standoff between the claimed rights of the European Union and its member nations to establish health, safety, and labeling standards for GM crops in the face of U.S. allegations of illegal trade barriers against its bioengineered products. The U.S. agro-biotechnology industry claims its products are demonstrably safe and rigorously regulated. With this global controversy in the backdrop, we shall examine the guiding principles and methods applied by the U.S. Food and Drug Administration (FDA) in its health assessment of GM foods.

In 1994, the FDA issued a ruling that a GM tomato known by the trade name the Flavr Savr was as safe as traditionally bred varieties. The benefit of the Flavr Savr was that it ripened more slowly than its parental strain. It was genetically modified through a process called antisense technology in which the deoxyribonucleic acid (DNA) sequence of one of its genes was reversed. Reversing the DNA sequence of a gene that codes for the enzyme polygalacturonase reduces the amount of the enzyme produced by the plant cells. Because polygalacturonase is required for the synthesis of ethylene, a compound that is necessary for the degradation of pectin and the initiation of ripening, the rate of ripening in the Flavr Savr tomato slowed down. As a result, this GM tomato may be picked red off the vine, yet it remains firm and ripe for many weeks after harvest. This was the first GM whole food product marketed to U.S. consumers.

Since the approval of the Flavr Savr tomato, other GM food products, such as corn, soybeans, potatoes, papaya, and canola, have been cultivated and marketed, and many more have been field tested in the United States, where organized opposition to GM crops began in the late 1990s. But anti-GM food activism did not stop large-scale cultivation and sale of major GM staple crops such as corn and soybeans.

Some observers explain the different receptions to GM crops by arguing that Americans are more trusting than Europeans of their regulatory agencies. Others explain the differences by noting that Europe has been sensitized by a series of agricultural crises including Mad Cow and Hoof and Mouth Disease. In addition, European farmers are suspicious of the socioeconomic impacts on them of U.S. seed imports. Alternatively, U.S. regulatory agencies have been criticized for having too cozy a relationship with GM food

producers (Finding a future for GM crops 2001).

During the 1990s, U.S. regulatory agencies adopted the concept of science-based policy to emphasize that science alone, not politics or values, would be the basis of their decisions. Underscoring this principle, in 2000, the executive office of the president under William Clinton stated that the U.S regulatory approach to agricultural biotechnology applies principles of "sound science" to ensure that there are not unacceptable human health and environmental risks.

In this article, we examine the role that the FDA plays in the oversight of foods derived from GM crops. We discuss the policies promulgated by the agency that apply to GM products and examine the agency's use of science in assessing the health risks of GM food for two cases, the alteration of fruit ripening and herbicide tolerance. Finally, we discuss the shared responsibility of the FDA and seed developers in evaluating the risks of GM foods and the current state of science behind human health risk assessment.

FDA'S GM FOOD POLICY

The FDA has statutory authority under the Food, Drug and Cosmetic Act to regulate foods, human and veterinary drugs, health devices, and cosmetics. The agency's seminal ruling on GM foods was issued in its 1992 policy document (FDA 1992), where it stated that transferred genetic material into crops is "generally regarded as safe." In reaching this conclusion, the agency decided to treat traditionally bred and GM crops as comparable with regard to the possibility of creating human health risks.

In lieu of new regulations, the FDA introduced a consultation process for companies planning to introduce bioengineered food (defined as foods whose genetic components have been modified by gene transfer technology) products to the market. Developers are provided a flow chart indicating when consultation with the agency is desirable (Kessler et al. 1992). In June 1996, the FDA published a guidance document for industry on the procedures for consultation.

> Under the process, a developer who intends to commercialize a bioengineered food meets with the agency to identify and discuss relevant safety, nutritional, and other regulatory issues regarding the bioengineered food prior to marketing it. . . . A developer may initiate such a consultation early or late in the development of the food. (FDA 1997, 2)

The agency does not usually conduct a comprehensive scientific review of the data produced by the developer for products that are classified as generally regarded as safe. Rather, it reviews the information provided by the developer and decides "whether any unresolved issues exist regarding the food derived from the new plant variety that could necessitate legal action by the agency if the product were introduced into commerce" (FDA 1997). According to the FDA, consultation is completed when all safety and regulatory issues are resolved. The types of issues the agency considers unresolved include signifi-

cantly increased levels of plant toxicants or antinutrients, reduction of important nutrients, new allergens, or the presence in the food of an unapproved food additive.

No specific time frame is set for the FDA to complete its consultation with a developer. In its final stages, the agency issues a memorandum that either cites unresolved issues or declares the consultation closed. As of April 2000, the median time for the FDA to complete its consultation review was 155 days, and the average time was 175 days. Developers have the right to exempt sensitive business information in such consultations from Freedom of Information Act disclosures, but they must justify the exemptions.

Nine years after issuing its initial policy, the FDA reiterated its position that

> there is unlikely to be a safety question sufficient to question the presumed GRAS [generally regarded as safe] status of the proteins . . . when these proteins or other substances do not differ significantly from other substances commonly found in food and are already present at generally comparable or greater levels in currently consumed foods. (FDA 2001, 7)

This is usually referred to as the concept of substantial equivalence, by which the agency means the GM crop variety is sufficiently equivalent to its parental strain so as not to warrant any special risk assessment or regulatory intervention (Kessler et al. 1992, 1749). Generally, when foreign genes are added to a food crop, the product of those genes is not treated as a food additive unless there is evidence that humans might become sick or their health might be compromised from the proteins that are expressed.

PREMARKET NOTIFICATION AND DATA REQUIREMENTS

The consultation process, introduced by the FDA, was viewed by many stakeholders as insufficient to protect public health. In November 1994, an FDA advisory committee recommended amending the consultation process by having GM food developers submit safety and nutritional assessments to the agency prior to marketing a product (FDA 1994). A formal agency proposal for requiring premarket notifications of bioengineered foods was published on 18 January 2001 and is expected to be finalized in 2002. The proposed rule would require developers of bioengineered food to submit a scientific and regulatory assessment of the food 120 days before it is marketed (FDA 2001). The FDA also recommended that the developers of GM foods continue the practice of consulting with the agency before submitting the required premarket notice.

The new proposed FDA mandatory premarket notification rule (hereafter referred to as the Premarket Biotechnology Notification [PBN] rule), the first major policy change since 1992 (Kessler et al. 1992, 1832; FDA 1992, 22984), would apply to any plant-derived bioengineered foods that would be consumed by humans or animals.

Any change in the composition of a food product resulting from its genetic alteration, except for an

alteration that endows the plant with pesticidal properties that are regulated by the U.S. Environmental Protection Agency, falls under the jurisdiction of FDA's proposed PBN rule.

The proposed regulations include requirements that developers provide data and/or information comparing the composition and characteristics of bioengineered food to that of comparable food. These requirements are designed to better enable the agency to determine whether bioengineered foods comply with the standards for food additives under the Federal Food, Drug and Cosmetic Act. The data and information requested fall into five areas: (1) characterization of the parent plant, mode of reproduction, and history of development; (2) method of development, including the construction of the vector used in the transformation of the parent plant and a thorough characterization of the introduced genetic material (number of insertion sites, number of gene copies inserted at each site, information about DNA organization within the inserts, potential reading frames that could express unintended proteins in the transformed plant, data or information related to the inheritance and genetic stability of the introduced genetic material); (3) discussion of any newly inserted genes that encode resistance to an antibiotic; (4) substances introduced into, or modified (present at an increased level relative to the comparable food) in, the food; and (5) comparison of the composition and characteristics of the bioengineered food to those of comparable (nonbioengineered) foods as well as a narrative analysis that explains the basis of the notifier's view that the bioengineered food is at least as safe as the comparable food.

Given that the genetic alteration of the food can affect the expression of nontarget genes, the agency stated that "it is important therefore for developers to evaluate bioengineered foods from new plant varieties to determine whether the composition of the food has been altered" (FDA 2001, 44).

The FDA applies a comparative risk standard to judge the safety of the bioengineered food. The developer must establish for the agency that the bioengineered food is "as safe as comparable food" and, in addition, that it complies with all applicable requirements in the Federal Food, Drug and Cosmetic Act. Because there are naturally occurring toxicants in many plants (e.g., solanine in potatoes), the comparative risk standard compares the ingredients in the new food with those in plants that are common to the human diet. Increases in a toxicant can disqualify the genetic modification as generally regarded as safe. The notifier under the PBN rule must provide a justification for selecting a particular food or foods as the standard being used for comparison.

ACKNOWLEDGING THE COMPLEXITY OF GM PRODUCTS

Assertions made by the FDA in the PBN rule indicate a much more cautious and nuanced view of GM foods than appears in earlier agency documents, in particular its 1992 policy

statement. In general, the agency expects that relative to conventional methods of breeding, GM products "are likely in some cases to present more complex safety and regulatory issues than seen to date" (FDA 2001, 7). The agency anticipates that plant breeders will utilize recombinant DNA (rDNA) techniques to an increasingly greater extent. These techniques permit breeders to introduce into crops substances from a wider range of sources than can be introduced by traditional breeding or to modify crops such that substances are present at significantly higher levels than in conventionally produced foods (FDA 2001, 7-8). As a result, the agency believes there is greater potential for foods derived through rDNA technology to contain substances that would require premarket approval as food additives. For example, by increasing the range of potential proteins that can be introduced into food beyond that of traditional breeding, the agency believes there is an increased potential for introducing an allergen into a food product. Food from the bioengineered plant might produce an allergen not found in its conventional counterpart (FDA 2001, 8). The FDA (2001) also discussed the possibility of significant changes in nutrients and toxins present in foods as a consequence of rDNA technology:

> It is also possible with bioengineering that the newly introduced genetic material may be inserted into the chromosome of a food plant in a location that causes the food derived from the plant to have higher levels of toxins than normal, or lower levels of a significant nutrient. In the former case the food may not be safe to eat, or may require special preparation to reduce or eliminate the toxic substance. In the latter case, the food may require special labeling, so that consumers would know that they were not receiving the level of nutrients they would ordinarily expect from consuming a comparable food. (Pp. 43-44)

The FDA (2001) acknowledged that rDNA insertions may disrupt or inactivate an important gene or regulatory sequence that affects the expression of one or several genes when the gene is inserted into a genetically active chromosomal location. Breeders using rDNA technology cannot control the location in the plant genome at which genetic material will insert (FDA 2001, 10). A gene inserted in one segment of the chromosome may be expressed differently from the same gene inserted in a different location. This is called the "position effect" (Griffiths et al. 1996, 873). This phenomenon is not unique to genetic engineering but can also occur in conventionally bred crops.

The FDA (2001) also discussed the effect of mixing the DNA of species that are distantly related. In its PBN rule, the agency asserted that crosses between closely related species involving homologous recombination are unlikely to lead to insertional mutagenesis, which could result in significant changes in food characteristics. Wide crosses in conventional breeding, according to the FDA, have a much greater potential than do narrow crosses for introducing unintended traits that may alter the safety of the food (FDA 2001, 11). As rDNA technology is increasingly used to introduce multiple genes to generate new metabolic pathways,

unpredictable changes may result. The synthesis of new substances not normally present in the host plant may alter the composition of the food in a significant manner that may raise nutritional or safety issues (FDA 2001, 9). The FDA expects that with the increased introduction of multiple genes, unintended effects may become more common (FDA 2001, 10).

Developers who believe they have adequate data may begin the final stage of the consultation process by submitting to the FDA a summary of their scientific and regulatory assessment of the food. As of 25 February 2002, the FDA had reviewed fifty-three consultations. These were all completed under the voluntary consultation procedures and thus did not have to meet the standards of the proposed PBN rule. The agency believes that all developers of bioengineered foods commercially marketed in the United States have consulted with it prior to marketing their products. The FDA's consultations covered eleven different commodities such as corn, canola, rice, tomatoes, cotton, and potatoes. Also, eleven different types of modifications are represented in the consultations to date including herbicide tolerance, insect and virus resistance, delayed ripening, modified oil, and enhanced oleic acid.

PRODUCTS REVIEWED UNDER FDA CONSULTATION

The FDA's written consultation reports are approximately four to five pages in length. They discuss the data provided by the developer and summarize the developer's argument regarding the safety of the expressed proteins and any changes in the compositional analysis of the foods. The consultation reports contain a final sentence indicating whether the FDA considers its consultation complete. By reporting that the consultation is complete, the agency is implicitly stating that it has no questions or reservations about the science, that it is satisfied with the company's comparative risk statement, and that voluntary compliance has been met. Some examples will illustrate the types of scientific judgments employed in the process and how they relate to the critical perspectives on biotechnology.

Case 1: Genetic modification for delayed ripening

The first consultation for the delayed-ripening Flavr Savr tomato looked at intended as well as unintended effects. For the intended changes, the scientific review considered the genes and proteins introduced. For the unintended effects, the consultation considered any changes in toxicity for one known toxicant in the tomato. The oral gavage tests of whole plant material carried out by Calgene (not required by the FDA) examined other possible toxicants. The company's consideration of nutritional changes also took account of possible gene-gene interactions and positioning effects that may not be obvious from the vectors used or gene constructs introduced. The company introduced genes into the cells of the tomato that made them resistant to kanamycin and neomycin, two clinically used

TABLE 1
REPORTS USED FOR DELAYED-RIPENING GENETICALLY MODIFIED CROPS

Report Number	Consultation Date	Company	Crop
FMF 526	17 May 1994	Calgene	Tomato
02	19 September 1994	Monsanto	Tomato
03	20 September 1994	Zeneca	Tomato
07	4 October 1994	DNA Plant Technology	Tomato
14	22 February 1996	Agritope	Tomato
60	20 October 1999	Agritope	Cantalope

SOURCE: Lists of completed consultations on bioengineered foods (Food and Drug Administration 2002).

antibiotics. The outcome of the consultation was that Calgene filed for a food additive petition for the antibiotic-resistant markers.

In Monsanto's version of the delayed ripening tomato (see Table 1, 1994), it introduced genes that expressed two proteins. One protein called aminoglycoside 3'-phosphotransferase II was already reviewed by the agency, so the consultation was directed at the second protein called 1-aminocyclopropane-1-carboxylic acid deaminase, which was reported to be widespread in common yeasts and bacteria. This protein was analyzed for allergenicity and toxicity. To test the hypothesis that the GM tomato was not significantly different in composition from parental varieties, Monsanto carried out compositional analyses on whole fruits for the following: ash; fat; total protein; carbohydrates; vitamins A, C, and B6; folic acid; riboflavin; thiamin; niacin; calcium; magnesium; iron; sodium; phosphorous; fructose; glucose; sucrose; citric acid; malic acid; lactic acid; natural tomato soluble solids; pH; titratable acidity; lycopene; and tomatine content. The tests carried out thus go beyond the concept that the exclusive consideration for assessing risk is the introduction of new proteins since expression of those proteins would not alone account for the compositional changes studied.

In the delayed-ripening tomato developed by Zeneca Plant Science with the polygalacturonase gene (see Table 1, 1994), the company focused on data showing that the introduced genetic material was integrated into a single insertion site and that the inserts remained stably integrated through successive generations. The company also focused on the levels of expression of the protein aminoglycoside 3'-phosphotransferase II and the glycoalkaloid tomatine and did an analysis of vitamins A and C, calorie content, fat, sodium, carbohydrate, fructose, glucose, dietary fiber, protein, calcium, and iron.

Agritope's version of the transgenic tomato contained a gene (*Sam-k*) that expresses a protein that degrades S-adenosylmethionine—the pentultimate precursor in the ethylene biosynthetic pathway. This substance was new to fresh food and thus was analyzed by the company for its sequence homology to any toxin or allergen in three major

protein databases (see Table 1, 1996, 1997). Following its predecessors, Agritope also did an analysis of some nutritional components of the transgenic variety and compared it to the parental strain.

The risk assessments of the GM delayed-ripening tomatoes did not include any human tests. Currently, there are no standards by which human clinical trials would be required. The most obvious rationale for such trials would be based on a concern that a potential human allergen could be unwittingly introduced into the GM food.

Case 2: Genetic modification for herbicide tolerance

The purpose of introducing genes for herbicide tolerance into food plants is to give farmers the opportunity to use a broad-spectrum herbicide that can be sprayed for seasonal plantings. In June 1993, Monsanto initiated a consultation with the FDA for a GM soybean that was rendered glyphosate tolerant. Glyphosate is a popular low-toxicity herbicide. A conference meeting held on 19 September 1994, which included eleven Monsanto and thirteen FDA scientists, brought closure to the consultation. This review of the science policy issues raised in consultations over herbicide-tolerant GM plants refers to sixteen cases that include transgenic varieties of corn, rice, canola, sugar beet, soybean flax, and radicchio.

The data produced by the seed developer to address the safety of the transgenic variety depend in part on the crop because certain crops contain proteins (e.g., toxins) whose enhanced expression is known to be problematic. For others, it may be the oils from the seeds and not the leaves that are the primary consumer product. We start out with a set of generic questions about the safety of GM crops. As part of their consultations, seed developers who submitted data to the FDA responded to some of the questions listed below. In this review, we report only on how the questions pertaining to health assessment were framed. We make no attempt to critically examine the quality of the studies conducted by biotechnology companies.

As part of the GM crop characterization, companies described the number of genes expressed in the transgenic plant, whether the genes were stably integrated into the plant genome, and if so, for how many generations. Another frequently addressed issue was whether the plant was tested for stability of the genes. Aside from the new genes transferred for the desired phenotype (e.g., herbicide tolerance), companies also asked whether there were any other coding sequences from the vector incorporated into the plant genome and, if so, if they were expressed in the plant. Other questions included the following: In what parts of the plant are the new proteins expressed (leaf, whole plant tissue, grain, processed plant products such as oil)? Is the protein sequence expressed in the plant's pollen? What is the level of expression of the proteins?

Companies also considered the potential allergenicity and toxicity of the new GM foods. A number of relevant questions are considered in the

TABLE 2

REPORTS USED FOR HERBICIDE-RESISTANT GENETICALLY MODIFIED CROPS

Report Number	Consultation Date	Company	Crop
01	19 September 1994	Monsanto	Glyphosate-tolerant soybean
20	26 September 1995	Monsanto	Glyphosate-tolerant canola
23	17 March 1995	AgrEvo	Glufosinate-tolerant canola
29	12 December 1995	AgrEvo	Glufosinate-tolerant corn
35	6 September 1996	Monsanto	Glyphosate-tolerant corn
41	29 May 1998	AgrEvo	Glufosinate-tolerant corn
45	16 October 1997	Bejo Zaden	Glufosinate-tolerant radicchio
46	24 April 1997	AgrEvo	Glufosinate-tolerant canola
50	15 May 1998	University of Saskatchewan	Sulfonylurea-tolerant flax
51	10 February 1998	Monsanto	Glyphosate-tolerant corn
55	21 April 1998	AgrEvo	Glufosinate-tolerant soybean
56	28 September 1998	Monsanto	Glyphosate-tolerant sugar beet
57	5 August 1998	AgrEvo	Glufosinate-tolerant canola
63	30 August 2000	Aventis	Glufosinate-tolerant rice
64	13 October 1999	Rhone-Poulenc	Bromoxynil-tolerant canola
66	4 April 2000	Aventis	Glufosinate-tolerant corn

SOURCE: Lists of completed consultations on bioengineered foods (Food and Drug Administration 2002).

consultations. Is the expressed protein (the active agent that counteracts the herbicide) similar in amino acid structure (sequence homology) to known protein toxins or allergens? What databases are used to compare the potential sequence homologies? When the GM food (e.g., soybeans) is subjected to heat treatment, what concentrations, if any, remain of the expressed proteins? Is the expressed protein degraded like other dietary proteins, for example, rapidly digested in simulated gastric and intestinal fluid (of humans and animals), and at what pH value? Does the expressed protein show any signs of acute toxicity in a mouse oral gavage study? Does the protein have any other characteristics similar to allergenic proteins such as heat or proteolytic stability or high concentration in food? What is the dietary exposure to the expressed protein? Is the protein glycosylated (are there sugar groups added)? Has the GM food been screened against sera from allergic individuals (using a radioallergosorbent test)? Were there any subacute toxicity feeding studies in mice or other animals? Was the GM food tested on allergenic adults?

Genes that code for antibiotic resistance markers were commonly introduced into the vector transferred to the GM food for purposes of detecting whether the gene segment has been inserted into the genome of the plant cell. Several of the consultations that referred to transgenic food with resistance markers made no reference to the risks of having these gene products in the food (see Table 2, numbers 23 and 56). Of those that did refer to the risks of antibiotic

resistance proteins in the food, the general types of questions raised were as follows: Does the expression of the antibiotic resistance gene (ARG) appear in the leaves, fruit, or pollen of the plant? Will the ARG compromise the efficacy of antibiotic treatment? Will the ARG transfer to the microorganisms in the gastrointestinal tract or in the environment? Will processed food from the transgenic plant have the ARG protein? What is the contribution of the ARG protein from the transgenic crop to the total human diet? Has the FDA reviewed the ARG as a food additive? None of the consultations on herbicide-resistant plants indicated any problems with the ARG in the GM plant variety.

THE SCIENCE BEHIND GM FOOD SAFETY

Companies that have undertaken FDA consultation, at least those involved in delayed ripening and herbicide resistance, have all performed some compositional analysis of their GM plant products. In a simplified, reductionist model of the genome, there would be no reason to assess changes in the composition of a transgenic plant beyond the proteins specifically expressed by the foreign genes. A risk analysis based on this model would miss effects from gene-gene interactions and from promoters introduced into the vectors that cause gene expression; the position of the transgene may affect expression of the resident genes or their reading frame, resulting in altered gene products.

Typically, companies compare some number of compositional components in the GM crop with a nontransgenic variety. As an example, for canola (see Table 2, number 23), the developer compared seed composition of transgenic and traditional varieties for oil, protein, crude fiber content, and phytosterol levels; for sugar beet (see Table 2, number 38), calories, crude fiber, calcium, fat, protein, and amino acids; for corn (see Table 2, number 41), moisture, fat, protein, ash, carbohydrate, neutral detergent fiber, and acid detergent fiber; for flax (see Table 2, number 50), protein, moisture, oil, ether extract, fat, crude fiber, ash, amino acid composition, nitrogen, potassium, phosphorous, sulfur, calcium, magnesium, copper, iron, manganese, zinc, and boron. It is important to note that there are no published standards on what nutritional components developers should test or compare.

Some of the compositional analyses reported statistical difference in several components between transgenic and traditional varieties. When developers found significant differences in selected nutrients between transgenic and parental strains, they argued the foods were "substantially equivalent" when the nutritional constituents in the GM product fell within the ranges reported in U.S. Department of Agriculture tables for that product. Implicit are two different criteria for assessing the impact of the GM organisms, one focusing on nutrient changes in relationship to the parental plant and another focusing on changes in relationship to all known varieties of the plant.

Antinutrients are components in the food that affect the availability of important minerals or nutrients for the health of the organism. Several companies included in their consultation report to the FDA an analysis of antinutrients in transgenic compared to nontransgenic varieties. The questions underlying this analysis are (1) What are the levels of the antinutrients in the GM food? (2) Are the antinutrients subject to heat denaturation? and (3) How could a rise of antinutrients increase the risk of disease?

Each of the food items has a unique composition of minerals, nutrients, antinutrients, microtoxins, and real or potential allergens. None of the consultation documents prepared by the FDA provide a rationale for testing a set of food components in transgenic crops. Except for allergens, the FDA does not provide a methodology for testing food ingredients. In the proposed PBN rule, each company defines its own testing regime, "comparing the composition and characteristics of the bioengineered food to those of comparable foods, with emphasis on significant nutrients, naturally occurring toxicants, and antinutrients" and initiates its consultation with the FDA (FDA 2001, 29).

The developers depend on the FDA to review the antibiotic resistance markers as food additives, and they do not submit their own independent studies. Companies often refer to databases of structural proteins that are known to be allergenic or known to be toxic to ascertain whether there is any homology between them and proteins in the transgenic food. Some developers reviewed the composition of eighteen constituents in the food; others studied far fewer for their compositional analysis. A minority conducted feeding studies on rodents or chickens.

DISCUSSION

Early in the debate of GM food, policy discussions focused on whether regulators should consider the process by which plants were modified when assessing risks. Three National Academy of Sciences reports, published in 1987, 1989, and 2000, stated that rDNA methods do not result in any unique hazards associated with GM plants and that the new methods of modifying plants make no special contributions to product risks. Therefore, it was argued from a science-based standpoint that characteristics of the product and not the process should be the sole consideration for regulation. The "product versus process" distinction, however, was not shared by all scientists (Regal 1994). Furthermore, the National Academy of Sciences provided no empirical test of its thesis that rDNA techniques do not introduce any unique hazards. Nor did the academy clarify or define "unique" hazards.

The FDA's science-based approach to regulating the safety of GM foods has departed somewhat from its 1992 policy, which claimed that bioengineered plants were no more hazardous for human health than plants derived from traditional methods of breeding. Recent FDA policy statements are more nuanced. For example, one general principle

that seems to undergird the agency's current view of GM food states that when transferred genetic material encodes proteins that are common to the human diet, the risks are minimal. Moreover, the sexual compatibility of genomic material and expressed proteins between the parental donor and the host (GM) plant is relevant to the assessment of unanticipated risks. In science-based policy, as the science becomes more nuanced, it stands to reason, so should the policy.

During the early stages of risk assessment of GM crops, the factors of primary interest were the source genes and their expressed proteins, the vectors used to transfer them, and the host plant in which they are introduced. But as more science was published describing gene-gene interactions and viral recombination, and as more empirical studies disclosed changes in the plant phenotype that could not be accounted for by the newly transferred proteins, the FDA began to acknowledge that wider crosses have a greater potential than narrow crosses for introducing unintended traits that may be relevant to food safety. Once the FDA accepted the scientific result that genetic alteration of food can affect the expression of nontarget genes, it included in its recommendations to food developers that they evaluate any potential changes in the composition of GM foods even prior to the proposed PBN rule.

The concept of "substantial equivalence" (or "substantially similar") has been used by the agency in its policy and guidance documents (FDA 1992; Kessler et al. 1992). Because there are naturally occurring toxicants in many plants, the FDA promotes a risk standard in which the GM food components are materially equivalent to the parental crop. However, the term substantial equivalence is not operationally defined and thus leaves considerable room for interpretation and normative judgment (Millstone and Mayer 1999; Miller 1999). When has a GM food been significantly altered, and when is it substantially equivalent to its parent crop? To address these questions, developers, following FDA recommendations, select a number of nutrients for analysis in GM products scheduled for marketing and traditional food varieties. As previously discussed, companies that find a statistical difference between components of GM food and traditional varieties apply a second test that compares the nutrient levels in the former to the range of values reported in U.S. Department of Agriculture documents. Good empirical science (measurements of nutrient levels) matched with different operational criteria (definition of substantial equivalence) can yield different outcomes, both claiming to represent science-based policy.

The FDA's draft guidance document leaves to producers the responsibility for testing and providing the agency information demonstrating that a GM product is as safe as its conventional counterpart. Because the FDA assumes that products developed from transferred genes are generally regarded as safe, it will take action when it has evidence to the contrary, based on consultations

or independent scientific review from the open literature.

To date, no evidence demonstrates that risks associated with GM crops and foods will be greater or less than those associated with conventionally bred products. Conner and Jacobs (1999) provided persuasive arguments in support of the hypothesis that three types of generic hazards, which might occur due to transgene insertions, occur under conventional plant breeding practices. The authors stated that hazards might result from (1) the inserted gene(s) and expression product(s), (2) secondary and pleiotropic effects of gene expression, and (3) mutagenesis due to gene insertion. Although genetic engineering and conventional breeding techniques differ, their possible effects on the genome are not qualitatively different. Each of the hazards that the authors believe might result from genetic engineering could also result from introgression of chromosomal regions through breeding crops with wild or cultivated relatives or from chemical or radiation mutagenesis, both common practices in conventional breeding (Conner and Jacobs 1999; Bergelson et al. 1996). There is still continued debate among scientists over whether the use of genetic engineering will increase the frequency, expand the range, or affect the quality of the hazards within these generic groups. Those who question the hazard comparability of traditional breeding and genetic technologies claim that the latter, by transferring genes from unrelated organisms, disturb the "tight control of gene activity" that occurs in closely related coevolved systems (Antoniou 1996; Ho 1998). Conner and Jacobs (1999) agreed that there are health concerns associated with transgenic crops, but the authors believe that like the hazards resulting from traditional breeding, the hazards will most likely be discovered before the crops are marketed. However, there is no science backing their claim that "in most instances the possibility of secondary biochemical effects of gene transfer are less predictable for traditional breeding than they are for genetic engineering" (Conner and Jacobs 1999, 231).

Debate also remains as to how best to monitor pleiotropic effects and moderate risks associated with them. The reviewed literature suggests some approaches to evaluate human health risks. Many plant toxins have been characterized, and expression levels of these known toxins can be monitored. Novak and Haslberger (2000) reviewed U.S. and EU regulatory documents reporting on levels of nutrients and known plant toxins in GM crops and parental lines. The authors compared reported toxin levels with recommended standard concentrations and found that toxins in most GM crops fell within normal range. In one case, however, environmental stress led to levels of glucosinolates up to "72.6 μmol/g in meal" for both transgenic and parental rape plants (canola), significantly higher than the recommended "less than 30 μmol/g meal." This study suggests that toxin levels in plant varieties may be most accurately estimated through studies of plants grown under different environmental conditions. Novak

and Haslberger (2000) noted that the studies they reviewed did not always report on the same compounds because regulatory agencies did not provide standard risk assessment data requirements for each crop. Systematic assessment of levels of important nutrients and toxins would provide a means to assess some pleiotropic effects relevant to human health (Novak and Haslberger 2000).

Wal (2001) noted that characterization of novel food allergens resulting from pleiotropic effects presents an additional challenge over current difficulties in characterizing whether proteins new to the food supply are allergenic. New proteins introduced into the food supply can be evaluated to determine whether they share biochemical activity or sequence homology with known allergens. Novel protein expression due to pleiotropic effects may not be easily assayed, because these proteins may not be readily identified. How do you find something when you do not know what it looks like? The author noted, however, that emerging proteomic techniques, not currently available, would permit identification of total protein expression and activity that may assist in identification of such allergens.

In a major policy statement on GM food risk assessment (FDA 2001), the FDA did not mention the term "pleiotropic effects" once, but it did acknowledge that "unanticipated effects" may be more prevalent with bioengineered products. The FDA (2001) stated that the phenotypes of transgenic crops (e.g., allergenic characteristics) may be completely different from their parental strains. Under its draft premarket notification plan, the FDA requested information that presupposes its acknowledgment of pleiotropy and epistasis (defined as the capacity of one gene to modify the expression of another unrelated gene). The draft states,

> Characterization of the introduced genetic material, including the number of insertion sites, the number of gene copies inserted at each site, information on deoxyribonucleic acid (DNA) organization within the inserts and information on potential reading frames that could express unintended proteins in the transformed plant. (FDA 2001, 36)

Notwithstanding these requirements and the emerging science on plant genomics, the FDA (2001) stated, "There does not appear to be any new information that raises questions about the safety of bioengineered foods currently being marketed" (p. 6). The agency continues to support its 1992 policy that GM foods are generally regarded as safe and therefore do not require mandatory testing and labeling (FDA 2001, 36) while advising GM food producers to test their crops for nutritional variations, allergenicity, and toxicity.

The food safety assurances given by the FDA for GM products, including its new proposed policy of premarket data submission and notification, have not as yet resulted in international trade harmonization between Europe and the United States. Europe is holding out for mandatory health and ecological testing, as well as labeling, while the

U.S. trade representatives point to the safety record of GM crops and the many scientific organizations that have given assurances that said crops are as safe for consumers as traditional crops (Haslberger 2000). Barring a catastrophic event, it is unlikely that science itself will resolve the differences, which have more to do with transscientific principles, socioeconomic factors, and trust in institutions.

References

Antoniou, Michael. 1996. Genetic pollution. *Nutritional Therapy Today* 6:8-11.

Bergelson, Joy, Colin B. Purrington, Curtis J. Palm, and Juan-Carlos López-Gutiérrez. 1996. Costs of resistance: A test using transgenic *Aradopsis thaliana*. *Proceedings of the Royal Society of London, Series B* 263:1659-63.

Conner, A. J., and J. M. E. Jacobs. 1999. Genetic engineering of crops as potential sources of genetic hazard in the human diet. *Mutation Research* 443:223-34.

Finding a future for GM crops. 2001. *Nature* 414:1.

Food and Drug Administration (FDA). 1992. Statement of policy: Foods derived from new plant varieties. *Federal Register* 57:22984-23002. Retrieved from http://www.cfsan.fda.gov/~lrd/bio1992.html.

———. 2001. Premarket notice concerning bioengineered foods: Proposed rule. *Federal Register* 66:4706-38. Retrieved from http://www.cfsan.fda.gov/~lrd/fr010118.html.

Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition. 1997. Guidance on consultation procedures: Foods derived from new plant varieties. Retrieved from http://www.cfsan.fda.gov/~lrd/consulpr.html.

Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition, Office of Food Additive Safety. 2002. List of completed consultations on bioengineered foods. Retrieved from http://www.cfsan.gov/~lrd/biocon.html.

Food and Drug Administration (FDA), Joint CFSAN/CVM Advisory Committee Meeting. 1994. Procedures for industry-FDA interaction prior to commercial distribution of foods derived from new plant varieties developed using recombinant DNA techniques. Retrieved from http://vm.cfsan.fda.gov/~lrd/biopro.html.

Griffiths, Anthony J. F., Jeffrey H. Miller, David T. Suzuki, Richard C. Lewontin, and William M. Gelbart. 1996. *An introduction to genetic analysis*. 6th ed. New York: Freeman.

Haslberger, Alexander G. 2000. Monitoring and labeling for genetically modified products. *Science* 287:431.

Ho, Mae-Wan. 1998. *Genetic engineering: Dream or nightmare?* Bath, UK: Gateway.

Kessler, David A., Michael R. Taylor, James H. Maryanski, Eric L. Flamm, and Linda S. Kahl. 1992. The safety of foods developed by biotechnology. *Science* 256:1747-49, 1832.

Miller, Henry I. 1999. Substantial equivalence: Its uses and abuses. *Nature Biotechnology* 17:1042-43.

Millstone, Erik, and Sue Mayer. 1999. Beyond "substantial equivalence." *Nature* 401:525-26.

National Academy of Sciences, Committee on the Introduction of Genetically Engineered Organisms into the Environment. 1987. *Introduction of recombinant DNA-engineered organisms into the environment: Key issues*. Washington, DC: National Academy Press.

National Academy of Sciences, National Research Council, Committee on Genetically Modified Pest-Protected Plants. 2000. *Genetically modified pest-protected plants: Science and regulation*. Washington, DC: National Academy Press.

National Academy of Sciences, National Research Council, Committee on the Scientific Evaluation of the Introduction of Genetically Modified Microorganisms and Plants into the Environment. 1989. *Field testing genetically modified organisms: Framework for decisions*. Washington, DC: National Academy Press.

Novak, W. K., and A. G. Haslberger. 2000. Substantial equivalence of antinutrients and inherent plant toxins in genetically modified novel foods. *Food and Chemical Toxicology* 38:473-83.

Regal, Philip. 1994. Scientific principles for ecologically based risk assessment of transgenic organisms. *Molecular Ecology* 3:5-13.

Wal, J. M. 2001. Biotechnology and allergic risk. *Revue Francaise d'Allergologie et d'Immunologie Clinique* 41:36-42.