
Food biotechnology: is this good or bad? Implications to allergic diseases

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Background: Food biotechnology represents advancement in the traditional interspecies and intergeneric breeding methods for improving food supplies worldwide. With respect to safety, foods developed through biotechnology techniques represent one of the most extensively reviewed agricultural advancements in history.

Objective: To review the relevant issues with respect to foods from genetically modified crops and allergenicity.

Data Sources: To impart this information, the author will rely upon his experiences with investigations into food allergy and food allergens, participation in various workshops designed to determine allergenicity of novel proteins introduced into the diet, web sites, issue papers, and articles relevant to the topic.

Results: Given that there are no validated methods or models to determine potential allergenicity of novel proteins, criteria have been established based upon characteristics of known food allergens. The combination of genetic and bioinformatics information available from known food allergens applied to foods developed from genetically modified crops to avoid the inadvertent introduction of allergens into foods should pose no significant allergenic concern to individuals with a genetic predisposition to food allergy. Education and sound scientific evaluation provided to the consumer should alleviate any fear of emotionalism as implied by "Frankenfoods."

Conclusions: The estimation that more than two trillion transgenic plants have been grown in 1999 and 2000 alone, with no overt documented adverse food reactions being reported, indicates that genetic modification through biotechnology will not impose immediate significant risks as food allergen sources beyond that of our daily dietary intake of foods from crop plants.

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INTRODUCTION

Until the recent introduction of transgenic plants, all improved food was produced through imprecise, laborious trial-and-error methods of classical crossing and backcross breeding procedures. The production of transgenic plants through refined breeding and bioengineering permitted plant breeders to improve crops and foods by introducing a copy of a gene producing a specific trait. The gene itself, composed of DNA, can be copied from any organism (plant, animal, or microbe), opening a vast new source of specific traits that would not be available by conventional breeding methods. Although it is unreasonable and unscientific to expect an absolute standard of safety, methodologic steps are being developed to determine the potential risk of these products to human health. Regulatory agencies, such as the United States Department of Agriculture (USDA), Environmental Protection Agency (EPA), and Food and Drug Administration (FDA) in the United States are in place to assist manufacturers/breeders and developers in evaluating the safety of new substances in foods.¹ Similar organizations and agencies in other countries function to ensure the safety of their food supplies.² Recommendations for the evaluation of foods derived from biotechnology include comparison of characteristics of novel protein with known allergens (bioinformatics), including the amino acid sequence similarity, evaluation of heat denaturation, acid

hydrolysis, and the pepsin-resistance of the novel protein, and assessing the biologic activity of the novel protein to serum IgE from patients with allergies and using animal models.³

Food biotechnology questions that should be addressed include: is the controversy over the biotechnology process (genetic modification) or is it the product (food staple) that is important to the consumer? Are concerns with what is hypothetical or what is reality with regard to food safety, eg, without knowledge based on scientific data, are proclamations of foods from genetically modified crops to be "Frankenfoods" justified? Are different standards being applied to an issue, gene selection, that is and has been a process since the beginning of agriculture with the intention of obtaining optimal food sources? With the ability to now cross species lines, it is imperative that issues of biotech engineering be founded upon scientific facts and sound judgment to ensure that genetically engineered food sources remain within a reasonable degree of predicted safety. Are risks and benefits being addressed with equal representation, or are the "risk amplifiers" receiving undue publicity compared with the "risk minimizers" and the "benefits" of foods from genetically modified crops? Education, right to know, and choice offering to the consumer are essential for determining the fate of foods derived from genetically engineered crops based on both risk and benefit.⁴⁻⁹

BIOTECHNOLOGY

Bioengineering is the technique of removing, modifying, or adding genes to a chromosome to change the information it

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contains. The modern definition of biotechnology is the application of the techniques of molecular biology and/or recombinant DNA technology, or in vitro gene transfer (bio-engineering), to develop products or impart specific capabilities to organisms.¹ The Codex Alimentarius has further defined modern biotechnology as the application of: (1) in vitro nucleic acid techniques, including recombinant DNA and direct injection of nucleic acids into cells or organelles; or (2) fusion of cells beyond the taxonomic family that overcome natural physiologic reproductive or recombination barriers and are not used in traditional breeding and selection. By changing this information source in cells, organelles, plants, or animals, genetic engineering changes the type or amount of proteins an organism is capable of making with respect to the inserted gene as well as potential disruption of the normal metabolic and protein pathways of the host. These modern molecular breeding methods are being applied by agricultural biotechnologists (agribiotech) to introduce new crop varieties to which useful plant traits (insecticide resistance) or characteristics (better taste) are expressed.

The predominant issue is whether there is widespread knowledge and acceptance of our food products derived from natural (conventional breeding practices, including selection by natural mutation/recombination) vs biotechnology sources (genetic engineering based upon gene insertion and genetic-induced mutation/recombination).¹⁰ Conventional breeding is considered as gene selection at random, whereas genetic engineering is selection with prediction. Therefore, biotechnology-derived foods are but an extension of conventional breeding practices under a much better controlled introduction of genes into the genomic background of the recipient plant. Successful acceptance of foods derived through biotechnology will depend on adequate education and training of the public. This includes the participation by scientists and corporate researchers who develop new technology with the intention of bringing that technology to product development and the introduction of new food sources into the marketplace. At each step of development, programs should be evaluated by scientific peer review and regulatory agencies. Most importantly, the inclusion of debate and input from the following should be considered: societies and their concerns; farmers/physicians that supply the product in the real world need to address issues related to production/usage; and users should be informed consumers with respect to the technology and product development.

Food

Foods for a population change over time as food consumption patterns are altered by changes in the food supply, introduction of new foods (kiwi, tangelos, or foods from genetically engineered crops), and/or changes in the demographics of the population. These foods and new sources of commercially engineered food crops are introduced into different marketplaces throughout the world. Even with food safety evaluation systems in place, it is important that we recognize that food is not inherently safe. Many of our foods contain toxins,

known carcinogens, and other noxious chemicals that are regulated. For example, in conventional breeding and selection of our foods, new potato varieties are screened for solanine, a toxic glycoalkaloid chemical shown to increase birth defects. Therefore, new varieties with higher concentrations of solanine are not released into the market.¹¹

Recent trends in agribusiness/agribiotech food crops such as corn, wheat, and rice have been to increase crop production and yield. Future aims include "biofortification" (breeding of staple foods that are dense in minerals, vitamins, and nutrients) to fight disease and malnutrition.^{12,13} These crops are and will be regulated through coordinated frameworks administered by various agencies to ensure that our food supply is as safe as possible. Rigorous food, ecologic, and environmental safety measurements are being addressed by these agencies and although the breeding methods may be different, the regulatory process for foods are basically the same.^{14,15} Regulatory acceptance of new food products occurs when a food or food source is shown to be as safe as possible or safer than its conventional counterpart based upon "weight of evidence" on a case-by-case scenario. Although the final regulatory evaluation of safety is always comparative, it is the consumer that determines final acceptance of the food product. Thus, a dialog among producer, grower, and consumer is crucial to the success of new foods being accepted.

FOOD ALLERGY/FOOD ALLERGENS

Food allergy involves an abnormal immune response to normally harmless food or food component that is mediated by type 1 hypersensitivity (IgE-mediated) reactions, which can be divided into two phases: sensitization and the allergic response.¹⁶⁻¹⁸ Allergens, including food proteins, are molecules that induce the production of IgE, which in turn binds to mast cells and basophils (sensitization). Upon a subsequent exposure to the inducing protein or similar cross-reactive protein, the allergen cross-links allergen-specific IgE-bound to mast cells and basophils, causing mediator release (histamine) resulting in the symptoms (allergic response). Symptoms can range from mild lip swelling, itching, and tingling around the oral cavity (oral allergy syndrome) to life-threatening anaphylaxis if not treated promptly. Epinephrine is the immediate drug of choice followed by follow-up emergency care.

There are no validated methods or single characteristics that exist to define/predict the allergenic risk of novel proteins. Foreignness, molecular complexity, solubility, stability, and concentration characterize antigenicity/allergenicity of macromolecules. To date, there is not enough information about known food allergens and nonallergen food proteins to make predictions of allergenicity for novel proteins. However, when characteristics of known food allergens are examined, judicious applications of these characteristics can be applied to come to a reasonable decision regarding a novel protein's potential allergenicity. The single most prominent trait attributed to food allergens is protein stability, ie, heat stability and/or resistance to enzymatic degradation. There-

fore, the current predictive methods or the evaluation of protein allergenicity of food allergens has included the detection of intact and/or residual antigenic fragments after artificial digestion procedures as determined by high-performance liquid chromatography and sodium dodecyl sulfate-polyacrylamide gel electrophoresis/immunoblot analysis. Immunogenic responses in animals can contribute to determining potential allergenicity, eg, production of IgE and IgG with subsequent release of allergic immune mediators (histamine, tryptase, eosinophil cationic protein, and tumor necrosis factor α) from sensitized cells following animal sensitizations, which bypass the natural gastro-intestinal processing. Amino acid sequence homology studies and structural characteristics of known food allergens can be used as comparators to determine potential allergenicity profiles of novel proteins. These procedures represent artificial means for evaluating the potential allergenicity of novel proteins and do not necessarily predict allergenicity. Ultimately, the potential hazard will have to be based upon substantial equivalence, which allows regulators through a comparative process to analyze the difference between a traditional variety and the novel variety.¹⁴ Risk evaluation will have to take into consideration an acceptable daily intake based upon dietary exposure estimates of the novel proteins use in the diet. As in the identification of known food allergens, only clinical responses to the food from genetically modified crops will provide scientific certainty of the novel proteins allergenicity.

Approximately 200 of the thousands of food proteins humans consume as food are allergens.¹⁹⁻²¹ As of February 2000, more than 40 food allergens have been cloned, 7 of which are from peanut cotyledons or genomic libraries.²² However, it is often not possible to separate the protein causing the allergic response, considering both the complexity of the food source (only a few proteins of a food are usually allergenic) and the meal. Also, within a food-allergic group, for example, peanut-allergic individuals, the allergenic protein can vary, the sensitization threshold is not known, and the threshold level for inducing an allergic response is variable (nanograms to milligram quantities).^{23,24} Fortunately, relatively few individuals have food allergy, estimated worldwide to be 1 to 2% in adults and 4 to 6% in children.^{16,17} However, the range of symptoms, from mild oral symptoms to fatal anaphylaxis, warrants caution for introducing potential new sources of food allergens into the food-allergic population. Continued surveillance and documentation will undoubtedly identify additional proteins as allergens; however, the ability to predict allergenicity of novel proteins must rely on the characteristics of known food allergens.

It is therefore necessary to arrive at standardized methods and techniques that will determine the single most widely accepted trait of food allergens, protein stability. Unfortunately, there has been little advancement in this area from the time Drs. Steve Taylor and Sam Lehrer summarized their findings in 1996.²⁵ I quote from their article:

“Although the evaluation of the resistance to hydrolysis of proteins could offer valuable information regarding

the potential allergenicity of specific proteins, a rigorous protocol for such experiments has not been established. Ideally, this protocol would mimic digestive proteolysis and include tests on the isolated protein and the protein in the appropriate food matrix. The experience with the evaluation of the immunogenicity of partial whey hydrolysis in animal models dictates that extreme caution be used in evaluation of results obtained from such animal models. The development of further data on the comparative stability of food allergens vs other food proteins to digestion, proteolysis, and hydrolysis would be highly desirable to determine the ability of this tool for the evaluation of the potential allergenicity of specific proteins.”

What is relevant is to make the leap from simple artificial systems to confident statements on the enormously complex gastro-intestinal tract digestibility of novel proteins and their interaction with the immune system if such methods and assumptions are to be standardized and used. Careful consideration should be given to posttranslational glycosylation, structure, and function, eg, enzymatic activity, plant pathogenesis-related proteins, and contractile proteins (protein families). By better defining the limits within which these factors operate, we may be in a better position to identify and characterize the hazards and risks of allergic disease associated with novel proteins.²⁶ Other relevant factors that are known to be associated with sensitization include the level of expression, consumption quantities, bioavailability of biologic active components, interactive effect of diet, duration of exposure, age at which the food is introduced, pollutants that can effect on cytokine production (Th₁/Th₂ stimulatory effects), and biotransformation by intestinal microflora.

With regard to dose, there is no established threshold sensitization or allergic response concentration of individual known allergens than contribute to allergy.²⁷ Bessler et al²⁸ concluded that cow's milk, hen's egg, fish, and crustacea allergens are stable to heat treatment, with enzymatic hydrolysis with meat allergens being partially stable to heat treatment and susceptible to enzymatic hydrolysis. In this review, positive challenges with the milk-elucidating symptoms in double-blind, placebo-controlled food challenge ranged from 5 to 250 g; egg, 5 mg to 5 g protein; fish, 6 mg to 6.7 g; and crustacea, 4 to 6 g. Overall, threshold levels eliciting symptoms from double-blind, placebo-controlled food challenge ranged from 1 mg to 250 g. In addition, threshold levels were reported to be strongly dependent on the patient's individual susceptibility and the allergenic potency of the particular food. Using structural/functional information and exposure assessments of known food allergens, rational predictions about the potential allergenicity of novel proteins are possible.^{2,3}

Procedures and guidelines for testing allergenicity of food proteins have been proposed for the evaluation of genetically modified plants³¹ and endorsed by scientific (International Life Sciences Institute) and regulatory agencies (Food and Agriculture Organization/World Health Organization) and are continually being appraised and modified as new data

and concerns arise that could pose public health problems.^{3,32,33} In situations where a protein is not known to be allergenic, the nature of the protein is compared with general characteristics of known allergens.³ However, currently, simulated gastric fluid digestion and simulated intestinal fluid are not physiologic.³ Animal models have not been validated with respect to interspecies extrapolation to humans. Our knowledge is based on imperfect or biased knowledge from pure or enriched novel food proteins vs their presence in a normal diet. Careful consideration is still required to: (1) identify extent of health risk with regard to frequency and intensity; (2) define a reasonable level of food as problematic (sensitivity vs sensitization risks); (3) how much an exposure (parts/billion or nanogram levels) can be considered safe to at-risk populations? (4) Can an acceptable risk level be addressed? and (5) is there a margin of safety at which risk/benefit ratio is acceptable?

FOOD BIOTECHNOLOGY

The introduction of crops produced through modern biotechnology has been a controversial topic in the United States as well as in other countries.³⁴⁻³⁶ Scientists, government regulators, scientific societies and academies, environmentalists, and consumer advocates (pro and con) have expressed their opinions, often fueled by sensationalism in the press without the provision of sound science and good sense.^{10,37} Foods derived from conventional crop development (genetic manipulation by selective breeding and cross-breeding) are generally accepted as safe. Crop production intended for human consumption under these conditions have been bred to perform under typical agricultural conditions and have for the most part not invaded natural ecosystems or caused unexpected negative environmental impacts. Historically, agronomic characteristics such as phenotypic stability, yield in performance, pest resistance, and food quality characteristics, such as nutrient content, digestibility, taste, and appearance have been introduced using conventional breeding techniques and accepted without question by consumers.

During the mid-90s industry began to develop new plant varieties that would provide greater weed control based on the emerging molecular biology techniques. The first food product from recombinant DNA technology, genetically engineered chymosin (rennin) is used for making cheese and the Flav'r Sav'r tomato (Calgene, Davis, CA).¹⁹ This brought into practice a whole new area crop development and resources for foods derived from genetically engineered sources. Taking into consideration corn and soybean as our major biotech crops, tracking the processed food from genetically modified seed development to the consumer becomes labor-intensive. Biotech crops reaching a medium-sized food company will eventually be distributed to 1,000 suppliers, from which 8,000 ingredients will be developed and distributed to 30 processing plants ultimately resulting in more than 6,000 different finished products that will be delivered to the marketplace.³⁵ For example, corn and soybean ingredients can be identified in 75 to 85% of all processed foods.

This technology continues to show great promise; however, biotech crops/foods must be cost-effective to industry, be deemed beneficial/safe to the environment over time be stable to pest infestations, weather conditions, geographic regions, economic markets, and ultimately, be acceptable to the consumer. As genetic engineering progressed into the production of foods destined for the table, scientists, regulators, and policymakers discerned that the use of these powerful techniques to supply our food should be evaluated before widespread use. Controversy came about as critics questioned whether these new techniques were being adequately regulated and with the failure of industry and manufacturers to provide adequate education into the production methods used to provide a safer, more desirable food product.

BENEFITS

Discussions of benefits and risks of adopting genetically engineered organisms are highly polarized between pro- and antibiotechnology groups.^{5,38,39} Unfortunately, the benefits have been largely downplayed and underreported as result of "risk amplifiers," taking the momentum with Frankenfoods, as opposed to the "risk minimizers" and "benefits" groups professing the advantages of genetically modified foods. At the outset, biotech companies have profited by selling genetically modified seeds that are engineered for herbicide and pesticide resistance. However, increased nutrient content, resistance to frost, tolerance to salinity and drought, delayed ripening, and introduction of nutraceuticals and pharmaceuticals will also favor companies developing these traits in our food supply.

With respect to farmers, improved crop yields through use of seeds with enhanced resistance to pests/diseases/drought/salinity/frost/weeds will certainly increase their productivity and livelihood. These traits will provide benefits to the farmer, including less fuel consumption for farm implements and reduced usage of expensive biochemical agents (herbicides and pesticides) conventionally used to control of weeds through multiple applications. Reduced applications have been linked to both environmentally friendly (fewer application, less runoff) and reduced environmental dangers such as concerns of superweeds and ecologic imbalance. With respect to superweeds, there have been few reports of gene transfer to weeds or other plants above that of conventional bred seeds. Ecologic imbalance (eg, plant/insect tolerance) has been controlled by crop rotation, alternate use of nonbiotech and conventionally bred seeds to reduce insect tolerance, and the introduction of safe zones to decrease potential cross-pollination.

Insecticide usage is usually insect-specific, eg, *Bacillus thuringiensis* (Bt) corn for corn borers. The alarm raised to herbicide and insecticide usage endangering the monarch butterfly is controversial.^{40,41} Cross-pollination is unlikely as the pollination time frame is different for the milkweed and corn. Spaying affects all unwanted plants and insects, whereas, herbicide-/insecticide-resistant seeds can be engineered with a greater degree of specificity. This avoids overuse of herbicides and the protection of nontarget beneficial

insects. For dairy farmers, the use of recombinant bovine somatotrophin results in increased milk production without altering the quality and safety of milk from nontreated herds.

Consumers benefit by realizing foods with improved quality, processing characteristics, health, nutrition, enhanced nutritional value, better taste, and a wider variety of foods. Examples of foods with improvement qualities include delayed ripening of fruits (tomatoes), cholesterol-lowering margarines and oils, cereals with fortified minerals and vitamins, and the potential use of edible vaccines. The introduction of the beta-carotene biosynthetic pathway into rice endosperm by genetic engineering, its bioavailability, transfer into agronomically varieties, and risk evaluation are being investigated to defeat vitamin A deficiency.⁴² Human insulin is now grown and extracted from plants reducing the need to use animal sources that enhance the risk of adverse events. The list continues to grow and will only improve nutrient sources as well as improve the health of world populations in need of food and medicines. A precaution is that the consumer should be informed (“right to know”) and given the choice (“labeling”) of what products are being marketed through biotechnology.⁴³

Future benefits include allergen modification through antisense/cosuppression techniques in plants with known allergens and modification of allergens to non-IgE-binding proteins⁴⁴ and treatment with thioredoxin to reduce allergenicity.⁴⁵ Other benefits include increased nutritional availability through supplementation/fortification in dietary patterns and action as biosensors that will detect and monitor hazardous materials in our environment, eg, zebra fish could be used to determine dioxin and pentachlorophenol levels.

Future applications include improving flavor by understanding and modifying ester biosynthesis in fruits, improving health characteristics of certain crops by engineering and enriching them with flavonoids (protection against cardiovascular disease), and improving nutritional value of certain crop plants for both human and livestock nutrition by genetically modifying them to overproduce selected amino acids (human and monogastric animals cannot synthesize 10 of 20 amino acids and need to obtain these essential amino acids from their diets).⁴⁶ Future designs for molecular pharming using transgenic plants as “bioreactors” to produce therapeutic proteins (proposed levels of 10 kg/acre in tobacco, maize, soybean, alfalfa) and plantibody production (plant-produced monoclonal antibody, eg, anti-S mutans secretory IgA for prevention of dental caries in clinical trials) will benefit public health.^{47,48}

RISKS

Risks of foods from genetically derived sources have received greater publicity and decreased consumer confidence in regulatory agencies largely from the incidence of mad cow disease and the failure to educate the consumer on the safety measures needed for our food supplies. Although this was considered to be a European problem, concerned individuals, risk amplifiers, and consumer watchdogs alerted the public to potential problems that were largely unfounded and based

upon emotions (Frankenfoods) rather than sound science. Where risks have been identified, there have been resolutions and solutions are either in place or being introduced to minimize them. Risks such as horizontal gene transfer, which included the use of antibiotic markers used to trace engineered gene transfer that could potentially lead to antibiotic resistance in humans have been largely dealt with.⁴⁹ Other antibiotics not in human use and other means of gene transfer identification are now in use as a result of this unwarranted potential risk. With respect to environmental alarms, reduced usage of conventional spraying will reduce the use of pesticides, runoff of these agents, and their accumulation into our water or food chain supply. Concerns regarding the monarch butterfly⁴¹ and other beneficial insects have been analyzed and with results suggesting that plants and animals will be exposed to a much lesser array and lower concentration of pesticide usage. Specificity of action, degree of accumulation in the environment, bioavailability (concentration and buildup in the food chain), and reduced usage benefits far outweigh the risks imposed by using pesticide-resistant biotech food sources.

Although it is not inconceivable that the introduction of novel proteins could potentially introduce allergen alarms, a judicious analysis/comparison of the novel protein to known food allergens can be used to determine potential allergenicity.⁵⁰ However, decision trees designed to guide both biotech companies and regulatory personnel are in place to ensure that our foods remain as safe as possible.^{3,31–33} Two examples that the system works include the Brazil nut protein introduced into soybean and Cry9c protein introduced into corn. In the case of the Brazil nut protein, a gene expressing a protein that would increase the nutritional value of soybean was introduced through gene insertion. Before introduction into the marketplace, Nordlee et al⁵¹ determined that individuals with Brazil nut allergen would be at risk following the introduction of this protein into soybeans. Using the tree and serum from individuals with Brazil nut allergy, they were able to determine that the introduced protein was identified as the allergen. As a result, this biotech food source never reached the food shelves. Other biotech companies have reported similar cases; however, they are simply removed from production and go unreported.

With StarLink corn (StarLink, Morrisville, NC), Cry9c, a δ toxin from *Bacillus thuringiensis*, was introduced into seed corn DNA to provide corn borer resistance, increase crop production and offer an alternative insecticide to aid in preventing resistance to the overuse of other Cry δ toxins previously shown to be safe. Although Cry δ toxins (both as sprays and biotech-derived seed sources) have been and are in use throughout the agribusiness, Cry9c raised alarms with respect to potential allergenicity as a result of delayed acid and enzyme digestion and potential allergenicity (production of IgE) in a rat model. A report by Bernstein et al⁵² also raised some concern; however, to date no IgE to Cry δ toxins have been identified in exposed individuals working with Cry δ toxin sprays or from eating Cry9c StarLink corn.^{53–57} These

two examples clearly demonstrate that systems are in place to safeguard our food supply through vigilance from the time of conception of a potential biotech food source, eg, known or unknown allergen source defined in decision trees, to characterizing the novel protein for characteristics attributed to known allergens before being approved for human consumption.

RISK ASSESSMENT

The so-called irrational perspectives have long frustrated scientific culture and behaviors that they believe are displayed by members of the lay culture. Lay individuals castigate scientists for their apparent lack of understanding of what is most important in decisions about potentially risky technology. Risk is inherently subjective and cannot be measured “out there,” independent of society and differences in culture. Cross-cultural differences must undertake the conflict of weighing health, environmental and social benefits, and risks faced in the accelerating globalization of our world trade economy. Effective and responsible communication between industry, governmental regulators and the public will need to agree on an acceptable level of risk for specific products or technologies. The need is to come to rational solutions of “sound science” that is scientifically based with that of “the chance of injury, damage, or loss” as viewed by the consumer.^{58,59}

The scrutiny by which modern genetically engineered food sources in the United States reach the market is the responsibility of the Coordinated Framework for Regulation of Biotechnology established in 1986.¹ This framework fell under the auspices of the USDA (plant jurisdiction), the FDA (food and feed regulation for animal or human use), and the EPA (pesticide regulation and usage in plants). The USDA requires field tests to prove performance and buffer zones to keep transgenic pollen from nearby fields (a field green house); regulates importation, interstate movement, and environmental release of transgenic plants that contain plant pest components, licenses field-testing of food crop before commercial release (safe to grow); and requires that no significant effects on environment through gene passages to weeds and wild native plants are prevalent. The EPA addresses crops that produce insect-killing proteins (target vs nontarget insects), registers pesticides produced in transgenic plant before distribution and sale, and establishes pesticide tolerances for residues in food (environmentally safe). The FDA addresses food safety evaluation (toxicology, nutrition, allergenicity testing) and regulates food, feed and food additives modified through genetic engineering based upon food safety (safe to eat and issues of labeling). As often as not, agencies such as these are updated, and future regulations are put into place as new criteria become available to assist the regulators in their respective fields.

At each stage of regulation, the public is given an opportunity to provide their input, and as often as not, consumer advocates/watchdogs alert the public to potential risks as determined by their independent standards, based predominantly on opinion of the technique and not scientific merit or

fact of the product. That is not to say that industry and regulatory authorities are/were blameless in this controversy. The agribiotech industry failed to educate the public on the advancements made in genetic engineering techniques that were being used to generate and supply a cost-effective, environmental-safe, risk-evaluated, safe food product that had been deemed as safe as their conventional counterparts.

Sanders⁶⁰ reviews the hazard critical control point concept as it applies to all sectors of the food chain, focusing on identifying the main avenues of risk and tackling them. In a special issue of *Plant Journal*, Kuiper et al⁵⁶ reviewed the principles regarding evaluation of the food safety of genetically modified foods. Hazard identification and determining potential hazards in our food chain should be based on previous knowledge about our food and diet. Genetic material (RNA or DNA) poses relatively little concern because we eat plant and animal tissue containing these nucleic acids daily with additional sources of nucleic acids in our normal bacterial flora. These are readily digested and offer no serious threats to our health. Novel proteins, largely from nonallergenic sources are screened for chemicals, toxins, or antinutritional factors that may influence our health. The potential for a novel protein being an allergen represents but one hazard, with only a very few of the hundreds of thousands of (glyco)proteins in nature that have been identified as allergens. The inherent risk is extremely low even in common allergenic foods, eg, in peanut only a few proteins are highly allergenic.

With respect to dose response to allergens, there is some information of relationship between dose and allergic response (sensitivity); however, there is *no* information available on sensitization doses. Justified warnings “May contain peanut” will not help consumer and may cause more confusion and avoidance of essential dietary intake for children.⁶¹ Exposure cannot be predicted; most fatal anaphylactic events to foods are a result of “unknown” hidden allergen sources.⁶² Thus, awareness of a potential food allergy is not a guarantee of safety. Nature of hazard and risk of exposure will vary depending on the food being evaluated, degree of processing, and nature of genetic modification. Where foods evaluated as safe, food ingredients derived from them can have widespread use without need for further evaluation; however, this does not necessarily mean a protein cannot induce sensitization/allergic responses in genetically predisposed individuals.

Risk characterization for food allergy requires a reasonable threshold level and safety margin much like those used to predict carcinogenicity and toxicity. The problem resides in the fact that we have relatively little information on threshold levels for allergic responses but none for allergic sensitization. However, certain physical characteristics (bioinformatics) of known food allergens have been attributed to food proteins and used in making decisions for assessing potential allergenicity. The caveat remains that whatever criteria are applied to defining a protein as a potential allergen, exceptions can be found within known food allergens.

Table 1. Biotech Food Testing Methods

<u>Immunoassay strip test</u>	<u>ELISA immunoassay</u>	<u>PCR nucleic acid detection</u>
Robust, reliable, rapid	2- to 4-hour test	3-day test
Field test performance	Lab/field performance	Lab-based
Qualitative	Quantitative	Qualitative
\$3 per sample	\$2–4 per sample	\$125–300 per test

Abbreviations: ELISA, enzyme-linked immunoadsorbent assay; PCR, polymerase chain reaction.

RECOMMENDATIONS

Dialog of accountability needs to be forged between scientists and the public. Considerations should be made for protein evaluation using monoclonal and polyclonal antibody assays to detect and trace whole protein and degraded products in the source (crop) product (food). Nucleic acid determinations can be performed using Southern blot technology with the DNA transferred onto nitrocellulose and probed with oligonucleotides derived from the gene sequence. In each case, the detection devices need to be validated and reference standards made available.⁶³ Testing methods that are available and should be made available for surveillance purposes are identified in Table 1.

An information and communication technology-based multidisciplinary framework could be put into place to educate the public on foods from genetically modified crops enabling the agrifood industry to change the attitudes of high-tech/high-value business enterprises. Examples could be taken from other available sources. Computer-based dietary modeling in which databases from national food consumption surveys, inventory of food products, food composition, table and food recipes, raw and processed foods could be used address the source of biotech derived foods.⁶⁴ The basis for identity preservation in use for kosher and organic foods and for selective traits in wheat and corn could be applied for tracking and postmarket surveillance needs.

Tracking biotech foods has already been in place for some commodities such as Cargill's InnovaSure Program (identity preservation system for dry corn milling at Illinois), Cereal Mills (Paris, IL), which allowed provision of StarLink-Free corn, and Iowa Soy Specialties (Vinton, IA) which tracks and produces both genetically modified and nongenetically modified soybeans.⁶⁵ The latter two systems both met established 5% tolerance levels and found steady market sources. At each level, costs, capabilities, responsibilities, testing, and tolerance can be arrived by "mutual solutions" with the need to understand and share information across system participants, from producer to food manufacturer to consumer. These programs should start with a monitoring system: biotech gene and protein from seed, growing, harvesting, transportation, storage, and food marketing providing the right to know and choice enabling the consumer to make knowledgeable decisions on what they are eating.

CONCLUSION

The agribusiness and food industry must determine to what extent foods from genetically modified sources will affect

their credibility and liability upon the introduction of novel foods into the marketplace. All compliance and safety measures, based upon sound science, must be provided to regulatory agencies such as the USDA, FDA, and EPA or the counterpart agencies in other countries in association with educational promotions designed to alert/educate the public. The educated consumer, when provided with adequate and appropriate information, will ultimately determine the fate of the product.

An estimated 3.5×10^{12} transgenic plants have been grown in the United States in the past 12 years, with more than two trillion being grown in 1999 and 2000 alone. These large numbers and the absence of any negative reports of compromised biosafety indicate the genetic modification by biotechnology poses no immediate or significant risks and that resulting food products from genetically modified crops are as safe as foods from conventional varieties. Whether or not modified food allergens introduced into host plants using biotechnology means will produce hypoallergenic plants with the same nutritional quality and desirability is a major hurdle that must be met.

As scientist, we have the responsibility to respond to society's concerns and to explain the facts that emerge from our research in a meaningful and understandable way that society can appreciate. We must ensure that debates on controversial topics are addressed as facts, evaluated by peer and public review, not opinions.⁶⁶

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