

Biotechnology and Food Allergy

Ricki M. Helm, PhD

Address

University of Arkansas for Medical Sciences, Arkansas
Children's Hospital Research Institute, 1120 Marshall Street,
Little Rock, AR 72202-3591, USA.
E-mail: HelmRickiM@uams.edu

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The production of genetically modified foods for an increasingly informed and selective consumer requires the coordinated activities of both the companies developing the transgenic food and regulatory authorities to ensure that these foods are at least as safe as the traditional foods they are supplementing in the diet. Although the size and complexity of the food sector ensures that no single player can control the process from seed production through farming and processing to final products marketed in a retail outlet, checks and balances are in place to ensure that transgenic foods will provide a convenient, wholesome, tasty, safe, affordable food source. Ultimately, it is the responsibility of companies developing the genetically modified food to provide relevant data to regulatory agencies, such as the US Department of Agriculture, Environmental Protection Agency, and Food and Drug Administration, to confirm that the transgenic product is reasonably safe for the consumer, as zero risk from allergen sensitization is nonexistent.

Introduction

It has been suggested that the increased prevalence of food allergies is linked to dietary behavior based upon the world marketplace and the evolution of food technologies. Several new foods have been introduced into our diet through the globalization of the food supply and through recent advances in biotechnology. Using advanced biotechnologic procedures, crop and plant breeders have introduced disease resistance, increased yield, and improved nutritional value. 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, may 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. Products from these genetically modified plants may contain novel proteins that are a potential risk for allergenicity. 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 US Department of Agriculture (USDA), Environmental Protection Agency (EPA), and Food and Drug Administration (FDA), are in place to assist manufacturers/breeders and developers in evaluating the safety of new substances in foods. Recommendations for the assessment of foods derived from biotechnology include comparison of the amino acid sequence of the novel protein with sequences of known allergens (bioinformatics); 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 from animal models [1••].

Biotechnology

Biotechnology, which can be divided into classical and modern, is defined as the use of biological systems and/or living organisms (or their derivatives) to create new products. Classical biotechnology represents traditional breeding and cultivation, *eg*, crossing of cultivated plants with wild relatives to introduce genes for pest and disease resistance. Continued breeding under these conditions is in practice to obtain modification of a cultivated organism's genetic material for animal and human needs. Successful breeding is defined through phenotypic characteristics or nutritional value of the crop or food source. Additional procedures include inducing mutations through chemical or radiation treatment and selection of desired traits.

Recently, plant hybridization, using plant cell culture techniques and fusion of plant cells, has been used to produce new crops. For example, hybrids of broccoli and cauliflower have yielded a new crop, the broccoflower; hybrids of oranges and tangerines yielded the tangelo. All of these procedures are labor intensive and require prolonged periods of time for optimization. When considering modifications of genetic material, classical biotechnology manipulations have been practiced for years without the burdensome regulations for food safety with respect to allergenicity (Table 1).

Table 1. Classic genetic manipulations

Process	Description
Selection	Breeding for faster poultry maturation and increased egg production, pigs with leaner meat, cows that produce higher yields of milk, and cattle for beef production
Hybridization	Selecting the best plants for subsequent crop development
Fermentation	Selecting the best microbial strains for cheese, yoghurts, and fermented meats

Modern biotechnology uses procedures to genetically modify, or “engineer,” organisms through the introduction of genetic material from one species to another. Scientists are now capable of identifying and introducing genes that are responsible for specific traits. This involves the introduction of single or multiple genes as compared with selection by crossing/backcrossing different species, which introduces intact DNA with multiple genes. With modern biotechnology, genetically modified plants may be achieved through the use of selected genes from living organisms or biologic agents derived from other organisms. The new organism is referred to as a genetically modified organism (GMO) and has been defined as any “organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination” [2].

Two methods have been used to transfer DNA or genes from one organism to another to produce modified (transgenic) plants. A foreign segment of DNA is incorporated through either a natural system present in plants (transformation using *Agrobacterium tumefaciens*) or by particle bombardment (the “gene gun”). *A. tumefaciens* is a soil bacterium that causes gall disease in some plants by transferring DNA from the bacteria to the plant. Using genetic engineering, the disease-causing genes are removed and the transporting DNA system of the bacteria is used to insert foreign genes into plants. Particle bombardment involves coating gold or tungsten particles with DNA and shooting the coated DNA with a high-pressure helium or electric charge into embryonic plant cells. In this manner, DNA-coated particles enter the cytoplasm and the DNA is incorporated into the genome. In both systems, antibiotic-resistant gene markers that permit selection of the desired transgenic plant are incorporated. Embryonic plant cells must then go through a series of culturing and selection to ensure that the protein has been successfully transferred and has not significantly altered the natural characteristics of the plant. Once successfully grown in culture, plant cells are cultured to produce mature plants compatible for crop production.

Genetically Modified Foods

The use of biotechnology to produce genetically engineered foods potentially may provide greater yields of nutritionally enhanced foods; however, this technology has both critics and supporters [2–6••]. The products from crops receiving

the benefits of agricultural biotechnology have been appearing in the American and worldwide diet for a number of years. Insect-resistant corn and herbicide-tolerant soybeans appeared in the mid-1990s and have reached an estimated 30% to 50% of the total acreage planted. As a result, an abundance of food products prepared from corn and soybean are common in the consumer marketplace without any significant adverse health effects above the background allergenic state of these food crops. In the United States, more than 40 transgenic crops have been approved for marketing. Four different crops (oilseed rape, potato, maize, and sugar beet) have been grown in twelve different habitats and monitored over 10 years. In no case was the genetically engineered plants found to be more invasive or more persistent than their conventional counterparts [7].

The first recombinant DNA (rDNA)-modified food to come before the FDA was the FlavrSavr tomato (Calgene, Davis, CA) [8]. Scientists used rDNA techniques to introduce an antisense polygalacturonase gene into the tomato genome. A normally present gene in tomatoes, the polygalacturonase enzyme causes the breakdown of pectin in the cell wall of the tomato, resulting in softening of tomatoes. The antisense gene encodes an RNA that suppresses the production of this gene, which results in the slower softening of the tomato and prolonged vine and shelf life with enhanced flavor development.

The FDA has completed more than 45 consultations of foods derived from genetically engineered plants. Most plants have been modified for agronomic properties (*eg*, disease or insect resistance and herbicide tolerance), although some were modified for processing characteristics or modified oil compositions. Using rDNA techniques, genes encoding insecticidal toxins from the bacterium *Bacillus thuringiensis* (Bt) have been introduced into cotton, corn, soy, and potatoes to produce transgenic insect-resistant plants. Although Bt δ toxins have been used in sprays to control insects without any reported adverse effects in humans, the use of modern biotechnology permitted the isolation, modification, and transfer of the gene encoding the insect-specific toxic protein. Some genetically modified plants that have been produced as improved sources of foods are listed in Table 2.

Genetically Engineered Hypoallergenic Foods

In light of the shortcomings of hydrolyzed food formulas, food allergen-free sources produced by genetic engineering are being tested as hypoallergenic alternatives. Among

Table 2. Properties introduced into plants and examples of foods genetically modified through modern genetic manipulations

Property	Genetically engineered food source
Disease resistance	Virus-resistant squash, potato, and papaya
Pest resistance	Bt corn, soy, cotton, potato
Herbicide tolerance	Roundup Ready soybeans, glufosinate-tolerant corn, glyphosate-tolerant soybeans
Modified protein and oil content	Soybean and canola oil-producing varieties with healthier oil composition
Improved flavor	Transgenic tomato: FlavrSavr brand with delayed ripening gene insert that permits prolonged vine ripening and shelf life

Bt—*Bacillus thuringiensis*.

these aims are investigations seeking to identify mutant forms of fruits, vegetables, and seed crops. Mutants with a low content of the main 16-kDa rice allergen have been identified [9]. In addition to identifying mutant forms with reduced allergen content, two methods of silencing endogenous genes with allergenic activity using genetic modifications are under investigation. One procedure includes the production of a chimeric gene consisting of a powerful promoter with the gene of interest in the reverse orientation, the antisense RNA. The antisense RNA interferes with the accumulation of the sense RNA (normal) from the target gene in the plant preventing the sense RNA from acting as a template for protein synthesis. In this case, trans- or co-suppression by antisense technology has been successfully applied to turn off the activities of particular genes [10]. Nakamura and Matsuda [11] were able to produce transgenic rice that resulted in an 80% reduction in the 16-kDa protein. In the second procedure, co-suppression, one or more additional copies of all or part of the sense gene is reintroduced into the plant. In most cases, this leads to increased production of the alternate protein; however, in others, this leads to gene silencing with neither the endogenous nor introduced gene being expressed. Limitations of these procedures include incomplete suppression leading to reduced but not complete elimination of the protein, unavailable long-term plant stability studies, the presence of multigene family coding or multiple allergens in the source, and interference with the functional properties of the crop itself.

Alternative methods under investigation include the mutation of recombinant allergens to non-IgE-binding peptides. Based on sequence information, protein engineering could be used to design homologous, non-allergenic proteins with similar structures, stability, and biologic/functional properties. The approach has been successfully used to remove conformational epitopes from the major allergen of apple [12]. This also is the focus of investigations with the major peanut allergens, Ara h 1 and 2, for the production of a hypoallergenic peanut plant. Site-directed mutagenesis studies have been applied successfully to produce variants of the major allergens of peanut with reduced IgE reactivity but retained T-cell reactivity [13,14]. Alteration of the allergen gene sequence

that leads to non-IgE binding will be introduced into the peanut to produce a potential hypoallergenic peanut plant.

The hypoallergenic food sources will have to be assessed for safety under much more stringent controls as they already come from sources with known allergens. Requirements for confirmation of a food presumed to be hypoallergenic include the consecutive steps in Table 3, which are based on a review by Ortolani *et al.* [15].

Advantages of Transgenic Foods

The genetically modified foods approved in the United States and the European Union to date, like many crops previously developed using more conventional plant breeding techniques, have been introduced with improved agronomic or disease-resistant traits. Biotechnology does have the potential to produce foods that can be of a more direct consumer benefit.

Significant benefits will include increased productivity (*eg*, host plant resistance conferred by Bt significantly increased yields up to 8% in corn) and decreased use of pesticides (*eg*, reductions in amounts of pesticide applied was up to 40% in potato crop production). A combination of increased productivity and decreased pesticide use may be exemplified by the use of Roundup Ready (Monsanto, St. Louis) soybeans, which reduced the need for multiple herbicide applications, increasing farmer's yield and profits by \$14 per hectare [16]. Other benefits include enhanced quality and the development of nutritionally fortified sources of foods by adding vitamins, drugs, and minerals into crop varieties. Ye *et al.* [17] have successfully introduced three genes that encode enzymes necessary for the carotenoid biosynthetic pathway to produce β -carotene, the precursor for vitamin A, into the rice endosperm. Although the "golden rice" is not yet available for commercial use, it is regarded to be a significant factor in the elimination of vitamin A deficiency and night blindness in Asian populations. The development of plants expressing vaccine antigens ("edible vaccines") also is receiving considerable attention [18].

Crop varieties may be engineered with reduced levels of unhealthy oils, proteins, and starches. Soybean and canola varieties already are engineered to reduce levels of fatty

Table 3. Steps involved in preparation of hypoallergenic foods

Preparation of the hypoallergenic food source
In vitro verification of claimed hypoallergenicity (sodium dodecyl sulfate–polyacrylamide gel electrophoresis immunoblotting)
In vivo testing of the hypoallergenic food in sensitized animals
Skin prick test with the extract of the hypoallergenic food in sensitized subjects
In vivo verification by administering the hypoallergenic food openly and then by double-blind, placebo-controlled food challenge of sensitized subjects

acids. Genetically engineered crops for animal feed that will match an animal's feed amino acid composition with that of its own amino acid balance will lower overall feed requirements and reduce animal waste. A yet-to-be-proven benefit will be the development of hypoallergenic foods.

Disadvantages of Transgenic Foods

In the same way that ingested drugs can have some deleterious effects in humans that are complications to their beneficial effect, in the case of transgenic foods stemming from new biotechnology, a zero risk of adverse events is nonexistent [19••]. As in classical breeding, risks associated with genetic modification are unintentional modifications of the host genetic material potentially resulting in changes in food components, including toxicants and allergens. There are a number of risks that have been evoked, including allergy to products derived from transgenic crops, without having been proven (Table 4).

Regulatory System

In 1992, the FDA published a policy statement regarding food derived from new plant varieties (Federal Register, 57 F.F. 22984, May 29, 1992). The policy statement explains how foods and animal feeds derived from new plants, including rDNA techniques, are regulated under the Federal Food, Drug, and Cosmetic Act. Included in the policy are provisions of guidance to industry that describe a standard of care for ensuring the safety and wholesomeness of foods developed by rDNA techniques. In April, 1996, the FDA, EPA, and USDA hosted a "Conference on Scientific Issues Related to Potential Allergenicity in Transgenic Crops." Topics included plant breeding practices and biotechnology, allergenic foods, exposure and allergenic responses, T cell and B cell antigenic determinants, in vitro and in vivo diagnostics, and animal models. The conference members concluded that methods were available for assessing allergenic potential (*eg*, protein sequence, acid degradation, enzyme resistance, and heat stability) of known food allergens that may be used for evaluating new proteins.

Safety issues that are to be undertaken include the food crop that is being modified; the potential for any introduced genetic material to encode harmful substances; the safety of intentionally introduced substances, such as proteins, fatty acids, and carbohydrates; and the assessment of endogenous toxicants and important nutrients in the modified plant. The agencies principally involved in the decision-making process for the safety issues of our food supply are listed in Table 5.

Next Generation Genetically Modified Product Applications

It is likely that increasing numbers of genetically modified foods will emerge in the near future with a variety of modifications and associated benefits. The minimum requirement should be that the genetically modified food should be as safe as the original product and should present minimal threat to human health. While most products will be essentially equivalent to conventional foods, there may be justifiable claims of associated benefits to human health in the reduced use of pesticides or herbicides, or economic benefits such as reduced loss of food due to spoilage. It is possible to envisage other types of genetically modified foods with direct benefits. Genetic modification and modern biotechnology will touch the lives of most people in the areas of food, medicine, and environmental protection. More complicated modifications, such as gene stacking, in which several genes are incorporated, will be introduced. The future holds many possibilities, *eg*, it should be possible for scientists in the following fields to modify organisms to produce the following (Table 6).

Allergenicity

The issue of allergenicity of food proteins has been considered in some detail. It is acknowledged that genetically engineered foods share with products of conventional breeding the difficulty of predicting allergenicity of new or novel protein(s) incorporated into any food source. In attempting to predict the potential allergenicity of foods derived from genetically modified plants, animals, and microorganisms, the examination of a number of parameters that are common to many potential food allergens is required.

Allergenicity is partly due to the physiology of the gastrointestinal tract, in which there is an intricate network interaction between enterocytes, antigen-presenting cells, and the immune cells that govern the development of immune response to food antigens. Pathologic conditions and protein stability to intestinal and normal flora digestion may contribute to this complex interaction. Foreignness, molecular complexity, solubility, heat and enzyme stability, and protein concentration are characteristics that have been attributed to the antigenicity/allergenicity/tolerance of food macromolecules. Detailed

Table 4. Risks associated with transgenic foods

Risk	Mechanism
Antibiotic resistance	Food crops using gene markers resistant to antibiotics may transmit antibiotic resistance to other organisms, including humans
Human health	Introduction of novel proteins as allergens
Pleiotropic effects	Appearance of toxic substances by awakening silenced genes or altering metabolic pathways
Environmental impact	Target insect resistance; nontarget insect damage; herbicide resistance
Invasiveness	Creation of changes in the host genome that could enhance the organism's ability to become an invasive species; cross-pollination of selected traits into susceptible wild relatives

Table 5. US agencies responsible for food safety

Agency	Roles and responsibilities
Department of Agriculture	Requires field tests to prove performance and buffer zones to keep transgenic pollen from nearby fields (a field greenhouse); regulates importation, interstate movement, and environmental release of transgenic plants that contain plant pest components; licenses field testing of food crop prior to commercial release (safe to grow); requires that no significant effects on environment through gene passages to weeds and wild native plants are prevalent
Environmental Protection Agency	Addresses crops that produce insect-killing proteins (target vs nontarget insects), registers pesticides produced in transgenic plants prior to distribution and sale, and establishes pesticide tolerances for residues in food (environmentally safe)
Food and Drug Administration	Addresses food safety assessment (toxicology, nutrition, allergenicity testing); regulates food, feed, and food additives modified through genetic engineering based on food safety (safety to eat and issues of labeling)

Table 6. Future genetically modified food applications

Pharmaceutical and chemical production: transgenic animals producing therapeutic compounds in milk
Agronomic: environmental stress resistance to drought, salinity, cold
Food and public health: foods with increased nutrient value and reduced allergenicity
Medical: edible vaccines in plants
Industrial and environmental: textiles, fuel oils, bioremediation, and control

analysis of allergen structure has not revealed any common sequences, elements, or features that are distinctly associated with the development of the IgE response. Potential allergenicity of a protein needs to take into account a number of factors, including protein structure, dose and route of administration, abundance, and relatedness to known allergens.

In 1996, procedures and guidelines for testing allergenicity of novel proteins introduced into foods were proposed for assessing the genetically modified plant product [20]. These procedures were endorsed and updated by scientific/regulatory committees including the Food and Agriculture Organization (FAO)/World Health Organization (WHO) [21]. The Joint Consultation of FAO/WHO identified a number of relevant criteria that should be carefully considered when assessing the safety of novel foods (Table 7).

The consultation also stated that foods found to contain an allergen that was transferred from the organism providing the DNA should not be considered for marketing approval unless the foods can clearly be identified in the marketplace and this identity is not likely to be lost

during distribution or processing. Additional concerns included the introduction of a toxic product or a gene that may modify the allergenic properties of the crop as a food source. The Joint Consultation of the FAO/WHO met again in 2001 and updated its assessment of the criteria for predicting protein allergenicity [1••].

In most cases, the native protein is not available in sufficient quantities to perform all the tests necessary to determine its safety in the food source. Thus, investigators turn to the production of the protein through recombinant technology expressing the gene product in bacterial, yeast, or mammalian host systems. These recombinant proteins must bear the "standard equivalence" test marking that is equivalent to the natural protein. This allows the regulator—through a comparator process—to analyze the differences between a traditional variety and the novel variety, should there be any. If a new food or food component is found to be substantially equivalent to an existing food or food component (already on the market), it may be treated in the same manner with respect to safety. When substantial equivalence cannot be established, it does not necessarily mean that the food product is unsafe. In the

Table 7. Criteria for allergenic assessment of transgenic foods

Criterion	Comment
Source of transferred genetic material	Particular caution must be exercised if the source of this material contains known allergens
Sequence homology	The amino acid sequence of many allergens is readily available
Heat and processing stability	Labile allergens are those that can be easily destroyed by heating, enzymatic degradation, or other processes. Labile allergens that are eaten cooked or undergo other processing before consumption are of less concern
Effect of pH and/or gastric juices	Most allergens are resistant to gastric acidity and to digestive proteases
Prevalence in foods	For example, new proteins expressed in nonedible portions of plants that are not of concern in terms of food allergy

event no comparator is possible, the food source in which the product is expressed should be used as the comparator.

Although controversial with respect to clinical relevance, IgE-binding carbohydrate determinants, specifically, β -1,2-xylose and α -1,3-fructose, may play a prominent role in prediction of allergenicity. Recombinant transgenic proteins with putative *N*-glycosylation sites may be glycosylated with plant *N*-glycans. These proteins will thus be transformed by the plant into IgE-binding structures and will have a large influence on the selection of sera to be used for judging the potential allergenicity of the transgene-coded product.

Prediction of Allergenicity

No validated methods are in existence for evaluating or predicting the allergic risk of newly introduced proteins into foods generated by direct, indirect, or unintended effects of genetic plant modification, either through classical or modern biotechnology. It seems reasonable to state that allergenicity of a food protein cannot be predicted by the analysis of crude product, but that a physiologic basis of antigen transport and modification by the organism must be taken into account.

Ingested DNA, which is abundant in our foods, is highly digestible and has been determined to be safe regardless of its source [22]. Therefore, the safety assessment process should be focused on novel proteins from the introduced genes, taking into account the genetic source. Proteins, under physiologic conditions, as sources and amounts of antigenic material transported across the intestinal epithelium, are very small ($\approx 2 \mu\text{g/h/cm}^2$), but they can represent a constant stimulation to the underlying gastrointestinal immune system [23].

Pleiotropic effects of introduced novel proteins may effect the regulation and expression of other genes not related to the intended modification. Endogenous proteins and allergens may be increased or decreased as a result of novel DNA insertions into the plant genome. The insertion of new genetic material into the host genome may also activate silenced metabolic pathways, altering the chemical state of the food source.

In situations where a novel protein is not known to be allergenic, the nature of the protein is compared to general

characteristics of known food and inhalant allergens. Structural comparison including pepsin-resistance, B and T cell epitopes, function, and three-dimensional structure are taken into consideration. Databases are used for comparisons of sequences that may provide an indication of homology to known allergens. However, the absence of homology does not necessarily imply nonallergenicity. Data banks may only be used to determine linear, not conformational, epitopes. Protein families, such as protease and amylase inhibitors; seed storage, pathogenesis-related, calcium-binding, and lipid transfer proteins; lipocalins; and profilins, may be used as suggestive sources for allergenicity [24]. Pepsin resistance has been used as an identifying feature of allergens; however, the physiologic environments in which these proteins are tested do not mimic the gastrointestinal tract. The kinetics of pH and release of enzymes are difficult to reproduce, and the tests are largely performed on isolated proteins and do not take into account the food matrix or the diet. Moreover, conditions encountered in industrial processing, such as heat denaturation, are not taken into account. For example, IgE to milk proteins is specific to destructured and denatured protein [25]. Animal models are being investigated that may be useful in determining the health risk; however, interspecies extrapolations to the human allergic response may be difficult. No animal model has yet been validated for the purpose of predicting allergenicity of proteins.

There have been several proposals to use some form of postmarket surveillance to track the potential allergenicity of novel proteins introduced into the food market. Post-marketing in itself will be valuable only in identifying the existence of a problem without providing adequate solutions to the events that could lead to food allergy. Post-marketing surveillance will not identify the specific effect of the novel protein in a genetically modified food over the background of conventional foods. For example, not all corn products would be derived from Cry9C StarLink corn, as it would be mixed with other corn crops or set against a background of corn products not produced from transgenic plants. It is recommended that health monitoring be used to detect all events that change the population's state of health, to alert the public authorities,

Table 8. Genetic background that may contribute to allergy

Chromosome	Regulatory system	Other contributing gene factors
5 (gene cluster)	Cytokines IL3–5 and IL9–13	MHC II and HLA molecular structures
11	β -chain of the Fc ϵ RI	T cell receptor α -chain
16	IL-4R	
12	Stem cell factor, interferon- γ , STAT-6	

and to prepare appropriate measures or actions to deal with any reported adverse reaction. Institutions and agencies should be created specifically for this purpose.

Food Allergy and Food Allergens

Among the confounding factors that contribute to food allergy, a genetic predisposition and the environment play important roles in conjunction with the intestinal absorption, protein processing, and the immune system's response to dietary proteins. Food proteins follow a succession of structural modifications from the plant source to treatment by the food industry to the degradation by digestive enzymes and further processing by the intestinal immune system. As in other allergies, food allergy consists of two separate phases: 1) sensitization and 2) triggering of the allergic response. However, the same allergen is not required for both steps of food allergy. An extensive cross-reactivity between pollen and food allergies exists (pollen-food allergy syndrome) that has led to the classification of complete and incomplete allergens [26]. Complete allergens have the following distinct molecular properties: sensitization (the ability to induce the immune system to produce IgE antibody), elicitation (the ability to trigger allergic symptoms), and binding to allergen-specific IgE. An incomplete allergen is defined as a nonsensitizing protein; however, it is able to elicit allergic symptoms. To date, the available information on food allergens and nonallergen food proteins is not substantial enough to make reliable predictions for potential allergenicity for novel proteins.

Factors that contribute to sensitization type I hypersensitivity reactions include, although do not require, a genetic predisposition. The allergic state of susceptible individuals represents a complex genetic disorder with potential contributions from one or more of the genetic backgrounds listed in Table 8.

Additional factors that contribute to sensitization include the level of protein expression in the food source; consumption quantities, including bioavailability of active components and their interactive effect with diet; duration of the exposure; and age at which the food is introduced. Gut maturity and altered mucosal permeability in association with immune maturation of the gastrointestinal tract

also are important. Other factors that should be considered include the effects of proteins acting as adjuvants causing inflammation that could result in bystander proteins becoming allergen(s) and carbohydrate facilitation of lectins in transporting glycoproteins across mucosal membranes. Recent evidence suggests that the mode of the environmental exposure is a more relevant predictor of allergenicity than any intrinsic properties of the protein. Sensitization by the inhalant route is characterized by repeated exposure of low doses of allergen (1 to 10 μ g/y) [27]. In contrast, sensitization to foods involves repeated exposure to foods in which the allergen generally comprises a high proportion of the total protein [27]. Thus, considering the multiple factors for food antigen sensitization, it may be expected that the measurement of the potential allergenicity of a protein will be complex, involving multiple assays, with a zero risk of its allergenic predictability being nonexistent.

Conclusions

The decisions about the use of transgenic plants and GMOs should not be based upon unsubstantiated claims, half-truths, or emotions but based on scientifically validated information. Food safety is the concern of all interested parties, and there is a need to carefully evaluate the overstating of potential benefits and downplaying of potential risks. Neither the risks nor the benefits are certain or universal, and both should be taken into consideration and balanced as zero risk from allergenicity is nonexistent. There are two conflicting viewpoints concerning the potential risk of genetically engineered foods: protection based on nonexistent zero predictability of allergenicity and vigilance based on health monitoring once the product is in the food chain. There are no validated methods in existence for evaluating or predicting allergenic risk generated by direct, indirect, and unintentional effects of genetic modifications through classical or modern biotechnologic means. Basically, the food industry; regulatory agencies; and, ultimately, the consumer, who by choice will determine the fate of the transgenic food product as an acceptable food source, must carefully assess the risk-to-benefit ratio based upon sound science.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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