
Genetic modification of food allergens

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Objective: To review allergen risk evaluation for genetically modified foods and our ability to predict protein allergenicity, methods that are being used to develop foods with reduced allergenic activity, and clinical aspects relative to assessing potentially allergic patients.

Data Sources: Information was identified using the MEDLINE database for governmental, international, and industry organizations that have considered possible unintended health effects such as food allergy and how they can be avoided.

Data Selection: The author's knowledge of the field was used to select articles for inclusion in this review.

Results: Organizations have created a decision process that has generally been successful in avoiding development of products that cause allergic reactions. Since some proteins expressed do not have any history of human exposure, risk evaluation may be more of a challenge for them. Biotechnology has also been used to try to develop foods with reduced allergenicity, and in future years such products should yield safer foods.

Conclusions: Allergy risk evaluation for known allergens and genetically modified foods appears to be reasonable and provides assurance of food safety. Allergenicity evaluation of novel proteins is a more complicated process that needs to be and will be improved as our knowledge of food allergens increases. Biotechnology can be used to produce safer and healthier foods; for example, allergenicity of some foods may be reduced through biotechnology. The role of the health care professional in assessing allergic reactions to genetically modified foods is essential and should play a greater role in the interaction of consumers, industry, and regulators.

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INTRODUCTION

In recent years, there has been considerable interest in the use of biotechnology to improve our food supply. Although there is concern about such change resulting in unintended health effects,¹ our food supply has actually been changing for thousands of years, since primitive humans first cultivated wild grasses as sources of grain and domesticated animals for the production of meat, eggs, and milk as food sources (Table 1). During the last century, plant and animal food sources have changed through breeding programs. Poultry, one of the most expensive sources of meat in the mid-1940s, is now one of the cheapest. Hybrid grain varieties, developed during the so-called green revolution in the 1960s and 1970s, more than doubled grain production, particularly in developing countries, and contributed to the world stability and prosperity seen during the 1980s and 1990s.²

Such alterations in plants and animals that supply foods for human use, whether by domestication and cultivation techniques or breeding and selection methods, did not occur without substantial change. These effects were observed on the plant and animal species involved (Fig 1), in the environment, and clearly in human societies. These alterations in our food supply were due to the so-called old technology. What differentiates the old technology (conventional breeding methods) from the new technology (use of molecular biological methods to alter gene expression) is genetic engineering

or, as some call it, molecular breeding. This method can result in the selection and transfer of a specific gene from one species to another. Since this method can precisely determine the gene that is transferred, genetic engineering is more selective compared with other breeding techniques.

Proponents for the use of this technology in altering our food supply cite numerous realized and potential benefits to humankind, including less expensive and healthier foods, hypoallergenic foods, elimination of deficiency diseases, feeding the growing world population, reducing organic pesticide use, and reduction in loss of habitat. However, critics of this technology raise legitimate environmental issues and potential adverse health effects. A major issue has been the potential allergy risk of these new genetically modified products.^{1,2} This article discusses (1) allergen risk evaluation for genetically modified foods, (2) prediction of protein allergenicity and improved risk evaluation, (3) clinical considerations relative to allergy risk evaluation, and (4) development of allergen-reduced foods. Information was identified using the MEDLINE database for governmental, international, and industry organizations that have considered possible unintended health effects such as food allergy and how they can be avoided. The author's knowledge of the field was used to select articles for inclusion in this review.

ALLERGY RISK ASSESSMENT FOR GENETICALLY MODIFIED FOODS

What Makes a Protein an Allergen?

Even after years of investigation, the question, "What makes a protein an allergen?" is still difficult to completely answer. Clearly, much has been learned about proteins that cause

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Table 1. Crop Cultivation and Animal Domestication by Humans

Species	Date (bc)	Location
Wheat, barley	6000	Southwest Asia
Rice	4000	Asia
Corn, beans, squash, tomatoes	1500	Central America
Sheep	8000	Southwest Asia
Goat	8000	Southwest Asia
Pig	8000	Southwest Asia, China
Chicken	3000	Central Asia

allergy, particularly in the past 20 years (the current period dominated by molecular biology) compared with the previous 50 years. Food allergens are generally very hardy molecules that resist heating or cooking and proteolysis. However, there are exceptions, and some food proteins that are labile can still be allergenic, particularly food components that cross-react with those present in aeroallergens. Allergens are generally proteins that are not only stable molecules but also in abundance in a particular food. Again, this is not true for all food allergens; for example, Gad c 1, the major allergen in codfish, is not a major cod protein.^{3,4}

A number of plant-derived and some animal-derived allergens have been classified into defined groups of proteins based primarily on amino acid sequence similarities and biological function.⁵ Examples are found in the seed storage proteins (vicilins), structural proteins (profilins), and proteins related or involved in the defense of plants (pathogenesis-related proteins such as proteases, chitinases, and lipid transfer proteins).⁶ The classification and structure of these proteins can and will continue to be useful in predicting allergenicity of protein molecules.

In food allergy, type and dose of exposure are also important. This can vary from region to region and is affected by culture and societal rules and regulation. An example is the consumption of peanuts in the United States compared with other parts of the world. The fact that peanuts are roasted in the United States and that exposure can occur at a very young age seems to affect the development of resulting peanut allergy. Thus, although substantial progress has occurred in our ability to identify properties that suggest a protein's allergenicity, there are many other issues that must be considered.

Therefore, it is difficult to have rigid rules for predicting the allergenicity of a protein, particularly in those properties already identified in allergenic food molecules. However, with our current knowledge, we can better judge potential allergenicity of proteins, a process that will continue to improve as our knowledge of protein allergens increases.

Risks of Food Allergy

Food allergies occur in approximately 2% to 8% of the population; most food allergies are primarily caused by 8 foods or food groups.⁷⁻⁹ Most food proteins are not allergenic; generally, of the 20,000 or more proteins in a plant, less than

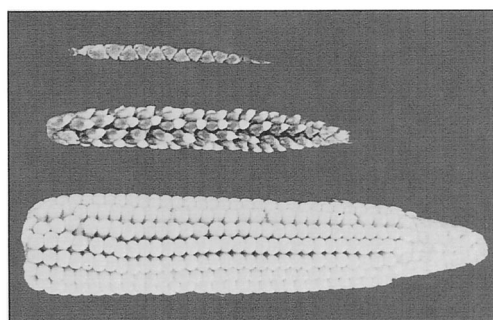
0.2% are allergenic.¹ Thus, the chances of being exposed to a particular food allergen or developing a specific food allergy are low. Despite this, misunderstandings persist with regard to development of food-induced allergic reactions. For example, the perceived prevalence of food allergies by the general population is approximately 25%; parents believe that 1 in 4 of their children have food reactions.³ A recent consumer survey regarding the prevalence of adverse reactions to foods indicates that 30% of those interviewed believed that they or some family member had an allergic reaction to a food product.¹⁰ Clearly, these figures are much higher than the actual prevalence of 2% to 8% mentioned previously.

Exposure requirements for development of sensitization to a particular food are not well understood by the public. At least 2 and probably more exposures are required to induce sensitization to a particular food; an allergen is not a toxin and thus does not cause a reaction without prior exposure (sensitization) of a susceptible individual. Thus, the risk of food allergy to the general population is considered to be low. However, obviously for the sensitized patient, the risk for food reactivity is high.

Genetically Modified Foods and Allergy

Early in the development of biotechnologic foods, a number of governmental and nongovernmental organizations have addressed the issue of allergenicity. In the United States, this has been the responsibility of the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and US Department of Agriculture (USDA). In Europe, several European Union agencies and individual governmental organizations within the member states have expressed concerns about allergenicity. Industry organizations such as the International Life Sciences Institute (ILSI), Allergy and Immunology Institute, and International Food Biotechnology Council and international institutions such as the Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO) have organized meetings of experts and advisory panels to address this issue.^{1,2} The involvement and interest of these organizations have resulted in a series of meetings to discuss an allergy risk evaluation for food products developed through biotechnology in the early 1990s that have continued through recent times. These discussions and interactions have led to the development of several approaches to risk evaluation as delineated in a decision tree.

When considering the potential alteration of existing allergens or induction of new allergens in foods, there are 3 possibilities that may occur. The first possibility is the potential alteration of levels of the endogenous proteins. If these proteins are allergenic, any increased concentrations of such molecules can be a major allergy concern. The second is expression of known allergens in other plant species. When a new protein is expressed in a particular source of food (ie, a soybean protein is expressed in wheat), since the soybean contains food allergens, it must be demonstrated that the soy protein expressed is not a soy allergen. The third possibility



Modern Maize and Tomato Compared with their Wild-type Ancestors

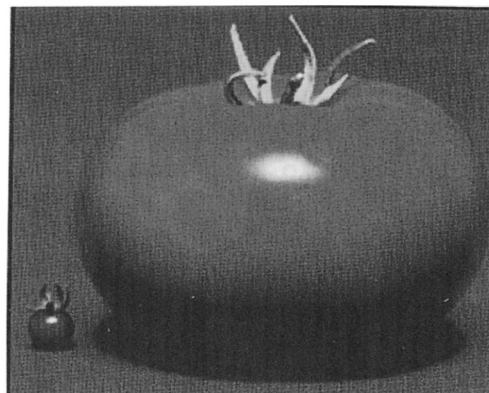


Figure 1. Comparison of modern maize and tomato with their wild-type ancestors. Throughout the millennia that these plants have been cultivated, there has been considerable change in the maize and tomato that we consume relative to its wild-type ancestor.

is the expression of novel proteins that may be allergenic. As the use of biotechnology increases and different proteins are expressed, such proteins may be derived from sources to which there is little if any prior human exposure. Thus, these proteins may be potentially allergenic, and the analysis and exclusion of them are more problematic for the food industry.

Evaluation of Genetically Modified Foods for Allergens

The first decision process ("the evaluation of allergenic potential of foods derived from genetically engineered crop plants") used in the evaluation of genetically modified foods was proposed in the ILSI monograph published in 1996.¹¹ This decision tree made the distinction between sources of genes from allergenic and nonallergenic plants. Known allergen sources can be tested by immunoassay, and depending on the result, product development can be stopped. The sources of genes from nonallergic plants may be evaluated by amino acid sequence comparison, stability properties, and resistance to enzymatic digestion compared with known allergens to determine if these are similar to allergenic or nonallergenic food molecules. Generally, this approach has served us well, since no new food products developed from genetically modified sources have been demonstrated to cause allergic reactions. Indeed, the development of an altered soybean was stopped when it was shown to express a major hazelnut allergen that could pose a substantial risk for nut-allergic individuals.¹² Subsequent meetings by the FAO and WHO (consultations in 2000 and 2001) and CODEX in Vancouver,

British Columbia, in 2001¹³⁻¹⁵ led to a modified decision process for assessing allergenicity to assist those developing and regulating genetically modified food products (Fig 2).

Since there has been little or no human exposure to novel proteins, a major challenge to the food industry and regulators has been to precisely assess the allergenic potential of these proteins. One approach has been to compare properties of novel proteins with those of known allergens. This approach has worked well thus far, but improvements can be made as our knowledge of food allergy and food allergens increases. Development of animal models of allergenicity may aid in this process.¹⁶

In recent years, several animal models have been investigated for stimulation of IgE antibody responses. Species used (rats, mice, pigs, and dogs), route of injection (oral vs parenteral), immunization methods (use of adjuvants or lack of adjuvant), and allergens tested (whole food, crude food extracts, purified food allergens) varied.¹⁶ All of these models have various advantages and disadvantages but certainly are providing important information with regard to the induction of a food allergic reaction and also the development of an animal model in which the allergenicity of novel proteins can be tested.² Recently, our laboratory investigated the allergenicity of major food allergen extracts in different strains of mice.^{17,18} Major food allergens, such as peanuts, shrimp, walnuts, and cashews, stimulated significant IgE antibody responses, in contrast to the lack of IgE antibody production

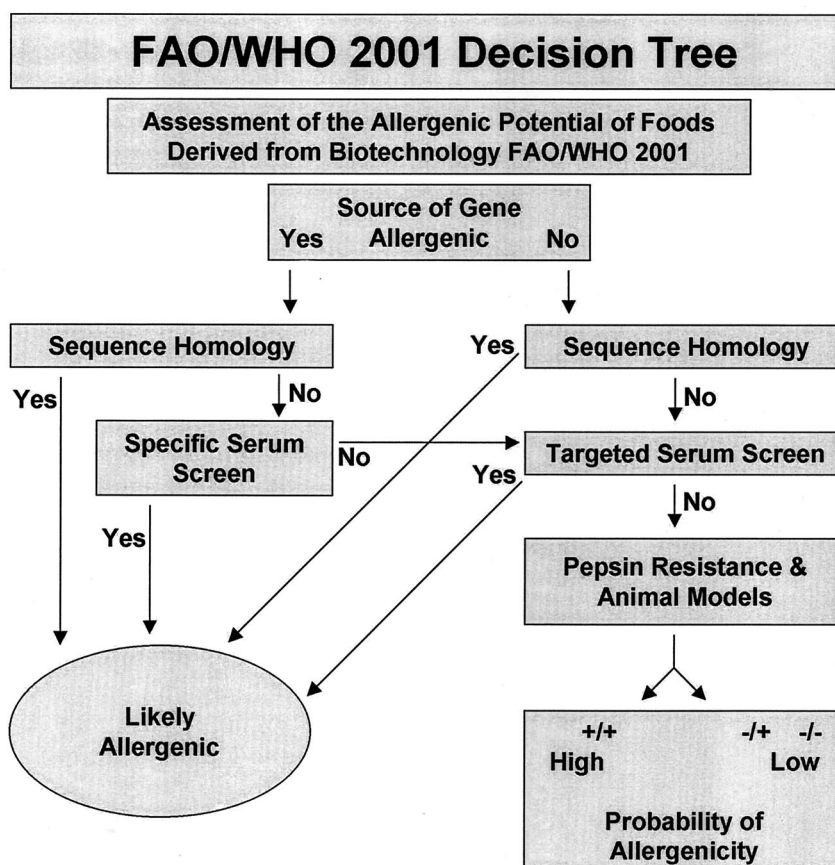


Figure 2. Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO) 2001 decision tree. Evaluation of the allergenic potential of foods derived from biotechnology.

or minimal production in mice immunized with less allergenic foods, such as rice, beef, and chicken (Table 2). The results are encouraging in that they suggest that mice may respond similarly to humans in terms of elevated IgE antibody reactivity to foods delivered through the oral route. Furthermore, analysis of IgE antibody reactivity to 2 major food allergens by immunoblotting (shrimp and peanuts) demonstrated substantial IgE antibody reactivity to major allergens within these foods, the same to which humans react. Thus, the results with this and other animal models encourage

us to be somewhat more optimistic about the development of such an approach for testing novel proteins in the future.

USE OF BIOTECHNOLOGY TO DEVELOP FOODS WITH REDUCED ALLERGENICITY

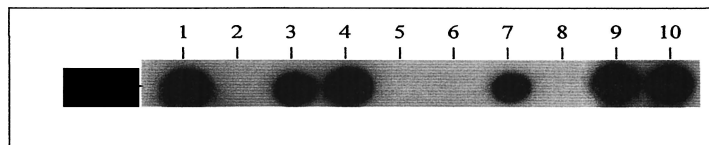
Biotechnology is being used in several ways to enhance the positive health effects of foods and reduce or abolish negative effects. For example, genetic engineering can be applied to reduce the allergenicity of a food by either reduction or elimination of a particular allergen through either posttranscriptional gene silencing or alteration of allergen structure in a way that reduces allergenicity such as a structural change to reduce disulfide bonds or modify genes that encode allergens. Examples of the potential of these techniques are found in studies to reduce the allergenicity of major peanut, soy, and shrimp allergens.^{1,2,19,20} A number of studies have shown that the major shrimp allergen (indeed a major or important allergen in most crustacean, arachnids, and insects) is the muscle protein tropomyosin.²¹ The sites on shrimp tropomyosin that bind IgE, the allergenic epitopes, can vary in size from approximately 8 to 15 amino acids. Using synthetic overlapping peptides and the SPOT system (Genosys, Wood-

Table 2. Mouse vs Humans

	Mouse IgE antibody	Human allergenicity
Peanuts	++++	++++
Shrimp	++++	++++
Tree nuts	++++	+++
Rice	—	+
Beef	—	—
Chicken	—	—

Abbreviations: plus sign, positive; minus sign, negative.

AA SUBSTITUTION IN EPITOPE 5b



Amino Acid Sequence									
Spot	266	267	268	269	270	271	272	273	
1	K	Y	K	S	I	T	D	E	WT
2	•	•	•	F	•	•	•	•	
3	•	•	•	•	•	C	•	•	
4	•	•	•	•	•	•	•	D	
5	•	•	•	F	•	C	•	•	
6	•	•	•	F	•	•	•	D	
7	•	•	•	•	•	C	•	D	
8	•	•	•	F	•	D	•	D	
9	•	•	•	•	•	S	•	•	WT
10	K	Y	K	S	I	T	D	E	

Figure 3. Amino acid substitution in epitope 5b. Epitope 5b was defined as a 8-long amino acid peptide in the carboxyl terminal portion of shrimp tropomyosin. IgE antibody reactivity to its sequence in shrimp tropomyosin is shown in spots 1 and 10. Substitution of this epitope with varying amino acids abolished IgE antibody reactivity (spots 2, 5, 6, and 8). This was shown to be essentially due to the substitution of serine (amino acid sequence 69) with phenylalanine. As few as 1 amino acid substitution can completely abolish IgE antibody binding.

lands, TX) of analysis, 8 major IgE-binding epitopes present in shrimp tropomyosin were identified. Analysis of the effects of amino acid substitution of these regions through use of synthetic peptides and the SPOT system identified mutated epitopes that profoundly affect IgE antibody binding.^{22,23} As few as 1 amino acid substitution can result in no change, enhancement, reduction, or complete abolishment of IgE antibody binding (Fig 3). Thus, such changes can produce a molecule inactive allergenically. If T-cell epitope sites are preserved, such molecules should still be active in desensitization of allergic patients while reducing the risk of an allergic reaction during treatment. Furthermore, incorporation of these mutations into the genome of allergens present in plants or animals may lead to the development of a product with reduced or abolished allergenic activity.

GENETICALLY MODIFIED FOOD ALLERGENICITY ASSESSMENT: CLINICAL CONSIDERATIONS

Despite assurances from manufacturers and government agencies, the development of risk evaluation processes, and even the fact that Americans have been consuming genetically modified foods for more than 10 years without any unintended adverse health effects, consumers from different parts of the world, particularly Europe, still express concern about the potential adverse reactions of genetically modified foods, particularly allergenic activity. Clearly, real or potential allergenicity of biotechnological foods and evaluation of possible allergic reactions are important issues for health care

professionals, especially those treating patients with allergic reactions, since they will (or should) be the first from whom the lay public will seek advice. Indeed, allergists have been an underused resource by consumers seeking more information about food allergy and the potential risks of newly developed foods. There are a number of issues that need to be addressed.

One must first diagnose whether a true IgE-mediated food-induced allergic reaction has occurred. Is this an immediate reaction? Are the reported symptoms typical of those of food allergic reactions? Has there been a prior exposure to this particular food? The diagnostic approach should be similar to that used for any food allergy, particularly one that is difficult to identify. A thorough history must be taken; IgE antibody reactivity using standard methods such as skin testing or in vitro tests must be determined; demonstration of reactivity to the particular food through an elimination diet and/or double-blind, placebo-controlled food challenge is required.

Diagnosis, however, may be difficult to achieve. Most reagents for testing allergic patients are produced from conventional food products and thus may not contain the novel proteins that are needed for allergen testing. There is variability of food products, since different modified grains are not segregated and thus the exposure to a different protein or altered food may vary. Hence, one might consider using different diagnostic procedures, such as the prick-prick test for altered fruits and vegetables (in which a needle is inserted into the fruit and then used to prick the skin of a potentially allergic patient), extracts prepared in the clinic for testing

Taco Shells and Related Yellow Corn Products: Consumer Contact Reports

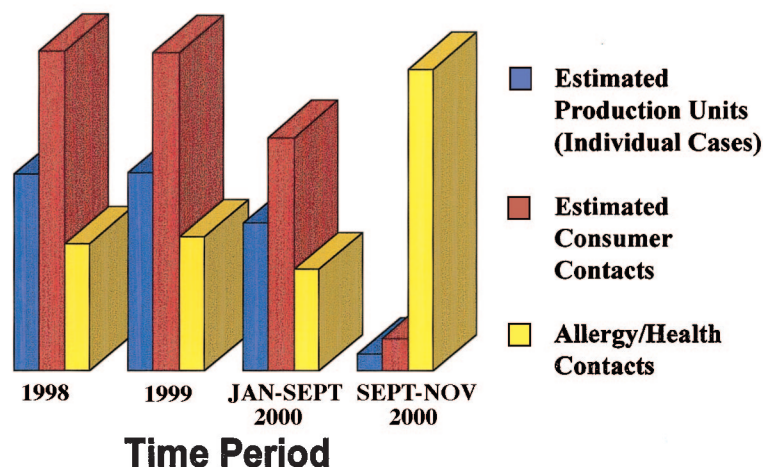


Figure 4. Taco shells and related yellow corn products: consumer contact reports. This information was obtained from the National Food Processors Association. It demonstrates that in timeframes of increasing planting and production of StarLink corn, steady or decreased consumer contact, and production units, there was no substantial change in allergy or health reports. However, in the 3-month period when it was discovered that StarLink corn contaminated the human food supply, there was a greater than 2-fold increase in the annual allergy health contacts within approximately a 3-month period.

patients, or a panel of foods to test patients with good histories of potential allergic reactions.

A number of difficulties may arise when diagnosing such allergic reactions. In light of events during the last several years, the media can have a major effect on the public's perception of whether a particular allergic reaction to a food product exists. For example, contamination of the food supply with StarLink corn was discovered and reported. StarLink corn, produced by Aventis (Research Triangle Park, NC), contains a stable insecticidal protein, Cry 9 c. Although allergenicity of Cry 9 c was never demonstrated, since it could not be disproved, StarLink was approved only as an animal feed.

In September 2000, this corn product was shown to be present in the human food supply, unleashing a barrage of media reports in which literally thousands of articles were published. To clarify this situation, the National Food Processors Association as requested by the FDA, EPA, and USDA obtained member company information that is reasonably related to StarLink corn exposure and alleged allergic reactions.²⁴ By gathering member information to estimate the amount of StarLink exposure through production units and consumer contacts and comparing this with allergy health contacts, it was clear that increased exposure to StarLink did not result in increased allergy or health reports by consumers (Fig 4). The major correlation of increase in allergy health contacts (approximately 3-fold for a 2-month period) com-

pared with the prior year's level was related to the period during which there was intense media reporting on StarLink corn. This suggests a positive association between the number of allergy complaints for processed food that contains yellow corn and the number of StarLink-related product recalls. Further investigation by the Centers for Disease Control and Prevention using a serological assay to measure IgE antibody to Cry 9 c supported the absence of an allergic reaction, although there were some concerns about the fact that a recombinant Cry 9 c protein of bacterial origin was used compared with one produced by plants. Recently, further support for lack of allergenicity for Cry 9 c was obtained when a patient who claimed to have had an allergic reaction to StarLink corn had a negative double-blind, placebo-controlled challenge result.²⁵

CONCLUSIONS

In summary, food allergy is a relatively rare disease whose causes can be misunderstood. Allergy risk evaluation for known allergens in genetically modified foods appears to be reasonable and provides assurance for food safety. Allergenicity evaluation of novel proteins is a more complicated process and needs to be improved as our knowledge of food allergens increases. Animal models show promise as an initial test for protein allergenicity. The role of the health care professional in assessing allergic reactions to genetically modified foods is essential and needs to be enhanced in the

interaction of consumers, industry, and regulators of genetically modified foods. The public must be better educated with regard to food allergy in general and the potential for developing allergic reactions to new products in particular. Furthermore, physicians need to be prepared to diagnose and treat any reactions that might occur, which is not an easy task. Finally, allergists can be an invaluable source of information on any potential allergic reactions to modified food products.

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