

Genetically engineered foods: implications for food allergy

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The products of agricultural biotechnology, including such common foods as corn and soybeans, are already reaching the consumer marketplace. Consumer exposure to such foods is already fairly significant, particularly in the USA. Thus far, no reports exist regarding allergic reactions to the crops that have been approved for introduction into the food supply. These crops have been modified to only a minor extent by comparison with their traditional counterparts, and the level of expression of new and novel proteins is quite low. Thus, consumer exposure to these novel proteins is very low and unlikely to result in allergic sensitization. Nevertheless, foods produced through agricultural biotechnology must be assessed for safety, including their potential allergenicity, before they may be approved by worldwide regulatory agencies for entry into the food supply. However, the adequacy of the current approach to the assessment of the potential allergenicity of foods produced through agricultural biotechnology has been the subject of considerable scientific and regulatory debate. *Curr Opin Allergy Clin Immunol* 2:249–252. © 2002 Lippincott Williams & Wilkins.

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Abbreviations

CP4 EPSPS	5-enolpyruvylshikimate-3-phosphate synthase from <i>Agrobacterium</i> sp. strain CP4
FAO	Food and Agriculture Organization of the United Nations
GTS	glyphosate-tolerant soybean
WHO	World Health Organization

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Introduction

Agricultural biotechnology has already had considerable impact on production agriculture and the food supply. The currently approved crops were engineered to have improved agronomic traits, such as insect resistance or herbicide tolerance, rather than any direct or noticeable consumer benefits. However, products with more noteworthy consumer benefits are in the developmental pipeline.

The number of crops that have thus far been commercially developed through agricultural biotechnology is relatively small, and include corn, potatoes, canola, soybeans, cotton, squash, and papaya [1•]. The impact of agricultural biotechnology on staple crops, such as soybeans and corn, has been especially significant on a worldwide basis, with 25.8 million hectares planted to transgenic soybeans and 10.3 million hectares planted to transgenic corn (maize) in the year 2000 [1•]. Those two crops have been especially successful in the USA, where planting of transgenic soybeans and corn have reached 30–50% of the total acreage planted to these crops. Fifteen countries have planted transgenic crops, although the USA, Argentina, and Canada were responsible for 97% of all plantings of transgenic crops in the year 2000 [1•]. The agricultural biotechnology industry has the potential to develop many more traits in these and other crops in the future. Expect to see additional crops that protect themselves from diseases and pests; crops that prosper under adverse conditions such as heat, cold, and drought; and crops that look better, taste better, and provide better nutrition.

Consumers, especially those in the USA, have been widely exposed to foods and food ingredients derived from crops produced through agricultural biotechnology. Corn and soybeans are particularly important foods, and many popular food ingredients, including corn oil, corn starch, corn syrup, soybean oil, and soybean lecithin, are derived from those two crops. In addition, canola oil and cottonseed oil are common food ingredients that would be derived from genetically modified crops.

Although exposure to foods and food ingredients derived from crops produced through agricultural biotechnology has been high, the impact of agricultural biotechnology on consumers has arguably not been largely visible because of the lack of readily apparent consumer benefits. Much publicity has recently surrounded the development of so-called golden rice with enhanced levels of vitamin A [2]. However, golden rice is not yet

available commercially, although it holds some promise to help eradicate widespread vitamin A deficiency and night blindness in certain Asian populations [3]. Agricultural biotechnology offers the promise of many more consumer benefits in the future, including improved quality characteristics, improved nutritional and health attributes, resistance to spoilage, and even reduced levels of allergens [4].

Safety of foods produced through agricultural biotechnology

The products of agricultural biotechnology should be subjected to a careful and complete safety assessment before commercialization. Regulatory agencies in many countries require agricultural biotechnology companies to conduct thorough safety assessments that are reviewed before the crop may be approved for commercialization.

Agricultural biotechnology involves the introduction of novel genes that confer desirable traits of various kinds. For genetically modified products, the safety evaluation focuses on the introduced trait or gene product. A thorough review of the entire safety assessment approach is beyond the scope of the present review. However, a more complete understanding of other safety concerns and approaches that relate to genetically modified foods can be obtained from other sources [5•].

Potential allergenicity of foods produced through agricultural biotechnology

The genetic modification of plants ultimately results in the introduction of a novel protein. The potential allergenicity of the newly introduced protein must be evaluated as part of the overall safety assessment. Although most allergens are proteins, only a few of the many proteins found in foods are allergenic under the typical circumstances of exposure. Thus, the probability that a specific novel protein in a genetically modified food product will be allergenic or become allergenic is rather low. However, the potential consequences surrounding the introduction of a novel allergen have dictated the assessment of the allergenic potential of all newly introduced proteins in genetically modified foods.

The development of foods produced through agricultural biotechnology involves a three-stage process [6]: gene discovery, line selection, and product advancement to commercialization. The allergenicity assessment of such foods should ideally begin at the gene discovery stage. For example, if the developer selects a gene from a known allergenic source, such as peanuts, tree nuts, or fish, then assurance must be sought that the gene product is not an allergen from that source. However, the allergenicity concerns may not always be so obvious. If

the novel protein belongs to a class of pathogenesis-related proteins that contains known allergens [7•], then the potential allergenicity of the particular novel protein becomes a relevant concern. For example, chitinase genes might be selected as a means to prevent various fungal diseases that are common in some crop plants, but chitinases from some sources are allergens [7•], and so the allergenicity of the particular chitinase must be assessed.

The development of approaches to assess the potential allergenicity of the novel proteins in genetically modified foods coincided with the development of agricultural biotechnology. In a classic report published in 1996 [8], the first scheme – a decision-tree approach – was introduced by a task force of the Allergy and Immunology Institute of the International Life Sciences Institute and the International Food Biotechnology Council. This approach was adopted in principle by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) in May 2000, at an expert consultation of the safety assessment of genetically modified foods [9]. In January 2001, the FAO/WHO convened an expert consultation that developed a somewhat different decision-tree approach to the assessment of the allergenicity of foods produced through agricultural biotechnology [10•].

All of those approaches relied on evaluating the source of the gene, the sequence homology of the newly introduced protein to known allergens, the immunoreactivity of the novel protein with serum immunoglobulin E from individuals with known allergies to the source of the transferred DNA, and the resistance to pepsin of the novel protein. Although general agreement exists on the elements of such approaches, considerable debate has ensued regarding the specific decision criteria [11]. The FAO/WHO decision tree included additional criteria, including the immunoreactivity of the novel protein with serum immunoglobulin E from individuals with known allergies to species that are broadly related to the source of the transferred DNA (targeted serum screening) and the immunogenicity of the novel protein in appropriate animal models. However, the Codex Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology held an ad hoc open-ended working group on allergenicity in Vancouver, Canada, in September 2001 [12]. It was concluded that targeted serum screening and animal models are not well developed approaches that can be immediately applied in a confident manner by worldwide regulatory agencies.

Although universal agreement has not been achieved on an optimal approach to the assessment of the allergenicity of genetically modified foods, general consensus does exist on many of the elements of such an

assessment strategy, including examination of the source of the gene, sequence homology, specific serum screening, and resistance to pepsin [13•]. Certainly, further modification of the allergenicity assessment approaches should be considered as scientific knowledge allows more accurate predictions regarding the potential allergenicity of novel proteins in humans. The scientific bases for the various tests advocated as part of these allergenicity assessment approaches are discussed elsewhere [14••].

Applications of allergenicity assessment strategies

There is no compelling evidence that any of the current products of agricultural biotechnology have resulted in allergic sensitization or allergic reactions among consumers. Those products with enhanced agronomic characteristics are nearly identical to their traditional counterparts, with the exception of one or more novel proteins that are expressed in rather low amounts.

Glyphosate-tolerant soybeans

The glyphosate-tolerant soybean (GTSs) has been modified to be tolerant to the broad-spectrum herbicide glyphosate, which allows for better weed control in soybeans. GTSs were developed with the insertion of a single gene that encodes for a glyphosate-tolerant 5-enolpyruvylshikimate-3-phosphate synthase from *Agrobacterium* sp. strain CP4 (CP4 EPSPS) [15]. GTSs are compositionally equivalent to conventional soybeans [16], and CP4 EPSPS is expressed at a rather low level in GTSs. With respect to allergenicity assessment, CP4 EPSPS was obtained from a bacterial source with no history of allergenicity. Furthermore, EPSPS is present in many plants, bacteria and fungi, and so related enzymes have been present in the human diet, apparently without consequence, for centuries. No sequence homology is found between CP4 EPSPS and known allergens. Additionally, CP4 EPSPS is rapidly digested by pepsin [17]. Therefore, GTSs containing CP4 EPSPS are unlikely to contain any novel allergens.

StarLink corn

Corn has been modified to be resistant to common insect pests by the introduction of several genes that encode specific proteins from *Bacillus thuringiensis* (Bt proteins) [18]. One of those products involved introduction of the *cry9c* gene, conferring resistance to Southern corn borer. That product, called StarLink (Aventis Crop Sciences, Raleigh NC, USA), has not been approved for human consumption anywhere in the world, but was approved for animal feeding in the USA.

Some StarLink corn was found in products intended for human consumption causing numerous recalls during the years 2000 and 2001. In terms of allergenicity assess-

ment, the *cry9c* gene was obtained from a bacterial source with no history of allergenicity. The Cry9C protein showed no sequence homology to known allergens. However, the Cry9C protein was resistant to pepsin hydrolysis under certain conditions. Thus, questions were raised regarding its potential allergenicity, and StarLink was not approved for human consumption. A few consumers have claimed possible allergic reactions to corn products contaminated with StarLink, but no evidence of Cry9C-specific immunoglobulin E antibodies was found in sera from those individuals. Thus, no proven allergies to StarLink corn exist. However, the resistance of the Cry9c protein to pepsin warrants some caution in the evaluation of its potential allergenicity and led a Scientific Advisory Panel of the Environmental Protection Agency to recommend its continued exclusion from foods.

Methionine-enhanced soybeans

During the early 1990s a high-methionine variety of soybeans was developed by Pioneer Hi-Bred International (Johnston IA, USA). Such soybeans would have nutritional advantages in animal feeding. High-methionine soybeans were created by inserting a gene from Brazil nuts that encoded a high-methionine protein. In terms of allergenicity assessment, this gene was obtained from a known allergenic source. The allergenicity of Brazil nuts was well established [19], but the identity of the allergens in Brazil nuts was not known. Using sera from individuals with Brazil nut allergy, Nordlee *et al.* [20] evaluated the possible allergenicity of the novel soybeans and the purified high-methionine protein. Specific serum screening showed that the gene obtained from the Brazil nut probably encoded a major Brazil nut allergen (*Be n* 1). This possibility was confirmed by positive skin-prick tests on three of the Brazil nut-allergic individuals [20]. As a result, Pioneer Hi-Bred International decided not to commercialize this variety of soybeans.

Conclusion

Food products and ingredients derived from genetically modified foods are widely available in worldwide marketplaces, and especially in the USA. No evidence exists of allergic reactions to any of the genetically modified foods approved for commercialization by regulatory agencies in various countries. Strategies do exist for assessing the potential allergenicity of genetically modified foods and the novel proteins contained therein. Although scientific debate continues regarding the optimal application of these strategies, the likelihood of the introduction of novel allergenic foods into the marketplace as a result of agricultural biotechnology remains rather low. In fact, commercialization of several products, including StarLink corn and high-methionine soybeans, were abandoned because of concerns regard-

ing possible allergenicity as a result of the existing assessment approaches. Few products of agricultural biotechnology (and none of the current products) will involve the transfer of genes from known allergenic sources, which is the most probable cause for concern. Applying the criteria recommended in the various allergenicity assessment strategies provides reasonable assurance that a newly introduced protein in a genetically modified crop has limited capability to become an allergen.

References and recommended reading

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