



Human health concerns with GM crops

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Abstract

Biotechnology was used in the first generation of so-called ‘GM’ crops to provide growers with complimentary and sometimes alternative crop management solutions to pesticides. Selected host genes or genes identified from other plants or non-plant sources are modified or transferred to a crop plant. The new or altered protein expression resulting from these modifications confer on the plant a desired physiological trait, such as resistance to particular herbicides or insect pests. Second generation modifications provide traits such as enhanced nutritional or health-promoting characteristics that are of benefit to consumers.

The commonly raised concerns about possible implications for human health are: inherent toxicity of the novel gene and their products, the potential to express novel antigenic proteins or alter levels of existing protein allergens, the potential for unintended effects resulting from alterations of host metabolic pathways or over expression of inherently toxic or pharmacologically active substances and the potential for nutrient composition in the new food occur differing significantly from a conventional counterpart.

Foods produced using biotechnology are subjected to far greater levels of scrutiny than foods produced by traditional plant breeding techniques. The accepted analytical, nutritional and toxicological methods employed to support this scrutiny and to assess and assure that a ‘GM’ food is as safe and nutritious as its ‘non-GM’ counterpart are discussed.

The challenges associated with identifying unintended effects in whole GM foods and the promise new (proteomics/genomic) technologies offer opposite traditional toxicity testing paradigms are appraised.

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1. Introduction

Crops developed through biotechnology have been marketed and used by farmers since the mid-1990s. Since 1996, there has been a 35-fold (1.7–58.7 million ha) increase in planting of transgenic crops. Five to six million farmers in 16 countries grow crops produced using biotechnology [1].

Biotechnology was used in the first generation of so-called ‘GM’ (genetically modified) crops to provide

growers with complementary and sometimes alternative crop management solutions to pesticides. Selected host genes or genes identified from other plants or non-plant sources are modified or transferred to a crop plant. The new or altered protein expression resulting from these modifications confer on the plant a desired physiological trait, such as resistance to particular herbicides or insect pests. Second generation modifications provide traits such as enhanced nutritional or health-promoting characteristics that are of benefit to consumers.

The following are the commonly raised concerns about possible implications for human health.

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1. Inherent toxicity of the novel genes and their products.
2. The potential to express novel antigenic proteins or alter levels of existing protein allergens.
3. The potential for unintended effects resulting from alterations of host metabolic pathways or over expression of inherently toxic or pharmacologically active substances.
4. The potential for nutrient composition in the new food occur differing significantly from a conventional counterpart.

2. Approaches for assessing inherent toxicity of the novel gene and their products

2.1. Inherent toxicity of the novel gene

The presence of foreign DNA sequences in food per se poses no intrinsic risk to human health by either direct toxicity or gene transfer [2,3]. This is a position consistently taken in the scientific community as a result of many years of research.

It should be noted that all foods contain DNA, which is ingested in significant quantities. In humans, dietary intakes of RNA and DNA vary widely but are typically in the range from 0.1 to 1.0 g per day [4]. Any concerns over the presence of novel DNA in a genetically modified food consumed in the human diet must take into consideration that this DNA would represent less than 1/250,000 of the total amount of DNA consumed. In view of this and the digestibility of dietary DNA, the probability of transfer of genes from genetically modified plants to mammalian cells is extremely low.

Despite this, the theoretical possibility of gene transfer and the resulting implications for human safety are often raised as a human health concern. To demonstrate that this will not happen is an extremely difficult, if not impossible, task. Examining scientifically what would be required for this to happen assures us that the probability of transfer of genes from genetically modified plants to microbial or mammalian cells is extremely low under normal circumstances of dietary exposure because it would require all of the following events to occur:

1. The relevant gene(s) in the plant DNA would have to be released, probably as linear fragments.

2. The gene(s) would have to survive nucleases in the plant and in the gastrointestinal tract.
3. The gene(s) would have to compete for uptake with dietary DNA.
4. The recipient bacteria or mammalian cells would have to be competent for transformation and the gene(s) would have to survive their restriction enzymes.
5. The gene(s) would have to be inserted into the host DNA by rare repair or recombination events.

2.2. Intrinsic toxicity of transgene product

The potential toxicity of the transgene product is considered on a case-by-case basis. Particular attention must be paid if the transgene produces a known toxin. A protein has the potential to exert health effects if it is not digested in the digestive tract and if it is absorbed systemically. This is illustrated by the intravenous toxicity of some well-known protein toxins (Table 1).

Protein toxins are known to act via acute mechanisms and at low doses [5]. Therefore, when a protein demonstrates no acute oral toxicity in high-dose testing using a standard laboratory mammalian test species, this supports the determination that the protein will be non-toxic to humans and other mammals, and will not present a hazard under any realistic exposure scenario, including long-term exposures. The acute toxicity of the protein expressed in a GM food is an essential component of the safety assessment of a GM food.

As discussed in the Society of Toxicology (SOT) Position Paper on the Safety of Genetically Modified Foods Produced Through Biotechnology [6], the safety of most Bt toxins is assured by their easy digestibility as well as by their lack of intrinsic activity

Table 1
Acute intravenous toxicity of proteins

Protein	Toxicity by intravenous route
Tetanus toxin	Death in mice, 0.2–1.2 mg/kg
Botulinus toxin	Death in mice, 0.00003 mg/kg Death in man, 0.00001 mg/kg
Clostridium toxin	Diarrhoea in man, 30 mg/kg
Ricin	Death in mice, 30 mg/kg
Cholera toxin	Diarrhoea in mice, 0.1 mg/kg

in mammalian systems. The SOT recognizes that the good understanding of the mechanism of action of Bt toxins and the selective nature of their biochemical effects on insect systems increases the degree of certainty of the evaluation of their safety.

3. Allergenicity

A food allergy involves an idiosyncratic reaction of the immune system to a normally harmless food or food component. Most food allergies are mediated by type-I immunoglobulin E (IgE) reactions. Food allergens induce the production of IgE that bind to the surface of mast cells and basophils distributed throughout the body. Subsequent exposure causes an allergic response (histamine release from basophils and mast cells) in a sensitized individual within minutes or, at most, a few hours. Antigenic proteins or glycoproteins typically range in molecular weight from ~10,000 to 70,000 Da and are stable to proteases and heat [7].

The percentage of proteins that are allergenic is very small. Only approximately 200 of the hundreds of thousands of proteins that humans consume in food are food allergens [8]. The 180 foods reported to be allergenic can be split into eight food groups (peanuts, soybeans, crustacea, fish, cow's milk, eggs, tree nuts and wheat) that account for 90% of all reported food allergies worldwide [8].

The potential consequences of food allergies for some people can be serious. Specific points relating to allergenicity of foods produced by biotechnology include:

- The possibility that genes from known allergens may be inserted into crops not typically associated with allergenicity.
- The possibility of creating new, unknown allergens by either inserting novel genes into crops or changing the expression level of endogenous proteins.
- The adequacy of screening methods to detect the creation of new allergens in transgenic crops.

3.1. Approaches to the assessment of food allergenicity

The International Food Biotechnology Council (IFBC) developed criteria and procedures to evaluate the safety of genetically modified foods. This led to

the adoption of a decision tree approach to food safety assessment that has been widely recommended and adopted by numerous regulatory agencies [9–11].

This was developed further by a panel of food allergy experts in the Allergy and Immunology Institute (AII) of the International Life Sciences Institute (ILSI) in collaboration with the IFBC. This decision tree process was published [8]. In March 2001, a new consultation by the FAO/WHO recommended significant additions.

SOT 2003 has summarized the main approaches outlined in these decision trees to evaluate allergenicity potential. The approaches include:

- Determinations of overall structural similarity of the protein of interest and known allergens.
- Sequence homology: using appropriate databases to determine whether the novel protein is similar to known allergens with respect to either overall amino acid homology, or with respect to discrete areas of the molecule where complete sequence identity with a known allergen may indicate the presence of shared epitopes.
- Serological identity: to determine whether specific IgE antibodies in serum drawn from sensitized subjects are able to recognize the protein of interest.
- Assessment of proteolytic stability: the work of some researchers, reviewed by Bannon et al. [12], in questioning the correlativity of digestion stability and allergenicity underpins the importance of using a weight-of-evidence approach that recognizes digestibility as only one of several criteria in assessing the potential allergenicity of a protein.
- Assessment in animal models: this is an area where significant research effort is being appropriately spent [13] and whilst there is no singly accepted or validated animal model predictive for the identification of protein allergens, progress is being made.

Testing strategies for allergens and protein allergy research is still evolving. The approaches outlined above, when used in combination and with the following knowledge, allow scientists to assess potential allergenicity:

- protein identity;
- protein source;
- previous dietary exposure;
- effects of processing/cooking.

4. The potential for nutrient composition in the new food differing significantly from a conventional counterpart

A key focus of substantial equivalence is a comprehensive comparison between the new crop and its traditional counterpart of key nutrients, toxins and other compounds that are naturally present. The genetically modified plant and its conventional counterpart is grown under a variety of field conditions to assess the composition under commercially representative growing conditions. The key components (e.g. protein, oil, carbohydrate, fibre, ash and minerals together with the key toxicants, anti-nutrients and allergens are assessed.

Furthermore, corn grain, whole plant green chop corn, corn silage, corn field residue, soybeans and/or soybean meal from the current genetically enhanced plants have been fed to chickens, sheep, beef cattle and/or dairy cows and compared with feeds produced from isolines of non-genetically enhanced plants. Results from 23 research trials [14] indicate that genetically enhanced corn and soybeans that are currently available in the marketplace are substantially equivalent in composition, are similar in digestibility and have a similar feeding value for livestock.

5. The potential for unintended effects resulting from alterations of host metabolic pathways or over expression of inherently toxic or pharmacologically active substances

Concern has been expressed about the potential for pleiotropic and insertional mutagenic effects. The former term refers to the situation where a single gene causes multiple changes in the host phenotype and the latter to the situation where the insertion of the new gene induces changes in the expression of other genes. Such changes due to random insertion might cause the silencing of genes, changes in their level of expression or, potentially, the turning on of existing genes that were not previously being expressed. Pleiotropic effects could be manifested as unexpected new metabolic reactions arising from the activity of the inserted gene product on existing substrates or as changes in flow rates through normal metabolic pathways [15].

5.1. Approaches to determining the potential for unintended effects

Although it is possible to envision situations where transgenic technology causes unexpected and potentially undesirable pleiotropic or mutagenic changes in the genome of the host, these cases are likely to be discovered before commercialization by the rigors of the event selection process:

- Agronomic characterization: morphology, yield and other agronomic parameters are a sensitive indicator of changes in the metabolism or physiology of a plant. Plants developed through biotechnology must meet very stringent agronomic and performance criteria that very effectively screens for unintended effects.
- Molecular characterization: the safety assessment requires that the DNA inserted into the plant is fully characterized and that newly produced proteins are clearly identified.

Equally important are the studies that are likely to be conducted on the selected event as part of the product development process, either to meet regulatory requirements or for good product stewardship. In addition to the comparative compositional analysis and livestock feeding studies, these can include:

- Laboratory animal feeding studies: where studies are considered necessary to assess the safety of long-term consumption of a food in the diet, sub-chronic study of 90-day duration is generally considered to be the appropriate duration to demonstrate the safety of repeated consumption of a food in the diet. The highest dose level used in any animal study should be the maximum achievable without causing nutritional imbalance while the lowest level used should be comparable to the anticipated human intake. A margin of safety may be estimated based on the absence or nature of adverse effects and likely human exposure. The need for additional toxicological tests should be considered on a case-by-case basis taking into account the results of the 90-day study and other studies. For example, proliferative changes in tissues during the 90-day study may indicate the need for a longer-term toxicity study.

With the advancement of new genomic, transcriptomics, proteomics and metabolomic techniques, collectively known as ‘omics’, consideration is being given for applying the non-targeted and simultaneous measurement, characterization and comparison of thousands of biological variables in plants to assess the potential for unintended effects. Recognizing the vast intrinsic variability in the context of many food constituents, a large number of observable differences between even genetically identical crops grown in different regions would not be unexpected. With this current data gap in base-line information for plants there is the potential for mis- or over-interpretation and subsequent misplaced safety concern.

Therefore, whilst this is proving to be an interesting area in technology development, as with any new method, this technology should be demonstrated to be robust, interpretable and reliable as well as being fully validated before it is used as part of the existing safety assessment paradigm for foods. This will require a great deal of collaborative work to determine how these methodologies can be applied in food safety assessment in a meaningful way.

6. Summary

Scientific evidence indicates that biotechnology-derived foods are as safe and nutritious as conventional counterparts. Using established and accepted methods of analytical, nutritional and toxicological research and the concept of substantial equivalence, the safety of current biotechnology-derived foods can be compared with that of their conventional counterparts. This approach has established that the level of safety to consumers of current genetically engineered foods is likely to be equivalent to that of traditional foods. The changes in the composition of existing foods produced through biotechnology

are limited and have no adverse nutritional or safety consequence.

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