

# **Society of Toxicology Position Paper**

## **The Safety of Foods Produced Through Biotechnology**

### **Executive Summary**

*The Society of Toxicology (SOT) is committed to protecting and enhancing human, animal and environmental health through the sound application of the fundamental principles of the science of toxicology. It is with this goal in mind that the SOT defines here its position on the safety of foods produced through biotechnology (genetic engineering). These products are commonly termed genetically-modified foods, but this is misleading since conventional methods of microbial, crop and animal improvement also produce genetic modifications and these are not addressed here.*

*1. There is no reason to suppose that the process of food production through biotechnology leads to risks of a different nature than those already familiar to toxicologists or that cannot also be created by conventional breeding practices for plant, animal or microbial improvement. It is therefore important to recognize that it is the food product itself, rather than the process through which it is made, that should be the focus of attention in assessing safety.*

*2. We support the use of the substantial equivalence concept as part of the safety assessment of biotechnology-derived foods. This seeks to establish whether the new food is significantly different from existing foods that are generally considered to be safe for consumers, and it provides critical guidance as to the nature of any increased health hazards in the new food. To establish substantial equivalence, it is necessary to conduct extensive comparative studies of the chemical composition, nutritional quality, and levels of potentially toxic components in both the engineered and conventional crop or animal. Any notable differences between the existing and new organism would require further evaluation to determine whether there is a likely to be a higher level of risk from the consumption of the foods derived from the engineered form. Through this approach, the safety of current biotechnology-derived foods compared to their conventional counterparts can be assessed with reasonable certainty using established and accepted methods of analytical, nutritional and toxicological research.*

*3. Extensive studies of this type have established that the level of safety to consumers of current genetically engineered foods is likely to be equivalent to that of traditional foods. Verified records of adverse health effects are absent, although the current passive reporting system probably would not detect minor or rare adverse effects.*

*4. The changes in composition of existing foods produced through biotechnology are slight. Assessing safety may be more difficult in the future if genetic engineering projects cause more substantial and complex changes in a foodstuff. Toxicologists are currently*

*limited in their ability to assess the risks presented by complex mixtures, and they have not yet developed methods by which whole foods (as compared to single chemical components) can be fully evaluated for safety. Progress also needs to be made in developing definitive methods for the identification and characterization of proteins that are potential allergens and this is currently a major focus of research. A continuing evolution of toxicological methodologies and regulatory strategies will be necessary to ensure that the present level of safety of biotechnology-derived foods is maintained in the future.*

## **Introduction**

The Society of Toxicology (SOT) is committed to protecting and enhancing human, animal and environmental health through the sound application of the fundamental principles of the science of toxicology. It is with this goal in mind that the SOT defines here its position on the safety of foods produced through biotechnology. In this context, biotechnology is taken to mean those processes whereby foreign genes (transgenes) are transferred to microorganisms, plants or animals employed in food production, or where the expression of existing genes is permanently modified, using the techniques of genetic engineering. We intentionally avoid using the term genetically modified organisms (GMOs) or foods in this context since conventional techniques of plant and animal breeding, which are not considered here, also involve genetic modification. The extent of the genetic changes resulting from such conventional breeding techniques, which is generally undefined, far exceeds that typically produced by transgenic methods. Consequently, it is important to recognize that it is the product, and not the process of modification, that is the focus of concern regarding the human or environmental safety of biotechnology-derived (BD) foods.

The principal responsibilities of toxicologists are to define and characterize the potential for natural and manufactured materials to cause adverse health effects and to assess, as accurately as possible, the plausibility and level of risk for human or animal health or for environmental damage under a defined set of circumstances. It is not the task of the Society of Toxicology to determine the overall value of a product or process by balancing health or environmental risks with potential benefits, or to choose between different strategies to manage risk, although toxicological considerations are important in both processes. Our purpose here is rather to identify and consider the primary toxicological issues associated with BD foods. Major areas of concern in the development and application of such foods in agriculture relate to the possibility of deleterious effects on both human health and the environment.

## **Types of Toxicological Hazards to Consumers and Producers Associated with BD Foods**

Current techniques of developing organisms used in the production of BD foods typically involve the transfer to the host of the desired gene or genes in combination with a promoter and a gene for a selectable marker trait that allows the efficient isolation of

cells or organisms that have been transformed from those that have not. Common selectable markers have included antibiotic or herbicide resistance.

Several key issues have been raised with respect to the potential toxicity associated with BD foods, including the inherent toxicity of the transgenes and their products, and unintended (pleiotropic or mutagenic) effects resulting from the insertion of the new genetic material into the host genome. Unintended effects of gene insertion might include an over-expression by the host of inherently toxic or pharmacologically-active substances, silencing of normal host genes, or alterations in host metabolic pathways. It is important to recognize that, with the exception of the introduction of marker genes, the process of genetic engineering does not, in itself, create new types of risk. Most of the hazards listed above are also inherent in conventional breeding methods and have historically been accepted with minimal public concern.

### The Concept of Substantial Equivalence

The guiding principle in the evaluation of BD foods by regulatory agencies in Europe and the USA is that their human and environmental safety is most effectively considered relative to comparable products and processes currently in use. From this arises the concept of "substantial equivalence." If a new food is found to be substantially equivalent in composition and nutritional characteristics to an existing food, it can be regarded as being as safe as the conventional food (FDA, 1992; OECD, 1993; Maryanski, 1995) and does not require extensive safety testing. Evaluation of substantial equivalence includes consideration of the characteristics of the transgene and its likely effects within the host, metabolic profiling, and measurements of protein, fat and starch content, amino acid composition and vitamin and mineral equivalency together with levels of known allergens and other potentially toxic components. BD foods can either be substantially equivalent to an existing counterpart, substantially equivalent except for certain defined differences (on which further safety assessments would then focus), or be non-equivalent, which would mean that more extensive safety testing would be necessary. The examination of substantial equivalence therefore may only be the starting point of the safety assessment. It provides a valuable guide to the definition of potential hazards from BD foods and illuminates necessary areas for further study (FAO/WHO, 2000). While there is some concern relative to the definition of the meaning of "substantial" and debate over the concept continues (e.g. see Millstone *et al.*, (1999) and following correspondence, and Royal Society of Canada, 2001), the concept appears to be logical and robust (FAO/WHO, 2000). If it can be established with reasonable certainty that a BD food is not more hazardous than its conventional counterpart, it provides a standard likely to be satisfactorily protective of public health. It is also an approach that has the flexibility to evolve in concert with the field of transgenic technology.

### Key issues with respect to human health effects of BD Foods

1. Is the transgene itself toxic? Can it be transferred to the genome of a consumer?

Humans typically eat several grams of DNA in their diet each day. Therefore, the transgene in a genetically engineered plant is not a new type of material to our digestive systems and it is present in extremely small amounts. In transgenic corn, the transgenes represent about 0.0001% of the total DNA (Lemaux and Frey, 2002). Decades of research indicate that dietary DNA has no direct toxicity itself. On the contrary, exogenous nucleotides have been shown to play important beneficial roles in gut function and the immune system (Carver, 1999). Likewise, there is no compelling evidence for the incorporation and expression of plant-derived DNA, whether a transgene or not, into the genomes of consuming organisms. Defense processes have evolved, including extensive hydrolytic breakdown of the DNA during digestion, excision of integrated foreign DNA from the host genome, and silencing of foreign gene expression by targeted DNA methylation that prevent the incorporation or expression of foreign DNA (Doerfler, 1991). Therefore, the possibility of adverse effects arising from the presence of foreign DNA by either direct toxicity or gene transfer is minimal (FAO/WHO, 2000; Royal Society, 2002).

## 2. Does the product encoded by the transgene present a risk to consumers or handlers?

The potential toxicity of the transgene product must be considered on a case-by-case basis. Particular attention must be paid if the transgene produces a known toxin (such as the *Bacillus thuringiensis* (Bt) endotoxins) or a protein with allergenic properties.

### 2a. Production of toxins

The level of risk of these gene products to consumers and those involved in food production can be and is evaluated by standard toxicological methods. The toxicology testing for the Bt endotoxins typifies this approach and has been described in detail by USEPA (2000, 2001). The safety of most Bt toxins is assured by their easy digestibility as well as by their lack of intrinsic activity in mammalian systems (Betz *et al.*, 2000; Siegel, 2001). However, each new transgenic product must be considered on its own merits based on exposure levels and its potency in causing any toxic effects, as is typical of current risk assessment paradigms for chemical agents.

### 2b. Production of allergens

Allergenicity is one of the major concerns about food derived from transgenic crops. However, it is important to keep in mind that eating conventional food is not risk-free; allergies occur with many known and even new conventional foods. For example, the kiwi fruit was introduced into the U.S. and the European market in the 1960's with no known human allergies; however, today there are people allergic to this fruit (Pastorello *et al.*, 1998).

The issues that have to be addressed regarding the potential allergenicity of BD foods are:

- do the products of novel genes engineered into food plants have the ability to induce *de novo* sensitization among susceptible individuals.

- do the products of novel genes have the ability to elicit allergic reactions in individuals who are already sensitized to the same, or a structurally similar, protein
- will transgenic techniques alter the level of expression of existing protein allergens in the host crop plant.

These are legitimate concerns and considerable scientific resources are being committed to determine the most appropriate and accurate approaches for identifying and characterizing potentially allergenic proteins. The first systematic approach to allergenicity assessment was developed by the International Life Sciences Institute (ILSI) in collaboration with the International Food Biotechnology Council and published in 1996 (Metcalf *et al.*, 1996). The hierarchical approach described therein has been reviewed and revised by the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) (FAO/WHO, 2001). The main approaches currently used in the evaluation of allergenicity are:

***(i) Determinations of structural similarity, sequence homology and serological identity:***

The objective is to determine whether, and to what extent, the novel protein of interest resembles other proteins that are known to cause allergy among human populations. There are essentially three generic approaches. The first is to examine the overall structural similarity between the protein of interest and known allergens. The second is to determine, using appropriate databases, 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. The third approach is to determine whether specific IgE antibodies in serum drawn from sensitized subjects are able to recognize the protein of interest.

***(ii) Assessment of proteolytic stability:*** There exists a good, but incomplete, correlation between the resistance of proteins to proteolytic digestion and their allergenic potential; the theory being that relative resistance to digestion will facilitate induction of allergic responses provided the protein possesses allergenic properties (Astwood *et al.*, 1996). One approach therefore is to characterize the susceptibility of the protein of interest to digestion by pepsin or in a simulated gastric fluid. However, this approach alone may not be sufficient to identify cross-reactive proteins with the potential to elicit allergic responses in food- or latex-sensitized individuals as in the case of oral allergy syndrome or latex-fruit syndrome (Yagami *et al.*, 2000). Nor are considerations of stability to digestion necessarily relevant for allergens that act through dermal or inhalation exposure and that may have significance for worker health.

***(iii) Use of animal models:*** Currently there are available no widely accepted or thoroughly evaluated animal models for the identification of protein allergens. Nevertheless, progress is being made and methods based on the characterization of allergic responses or allergic reactions in rodents and other species have been described (Kimber and Dearman, 2001).

Although testing strategies for allergens are still evolving and no single test is fully predictive of human responses, the approaches outlined above, when used in

combination, allow scientists to address questions of potential allergenicity and these will increase in precision and certainty with time. Considerations of this type led the US federal agencies to deny approval of StarLink corn for human consumption because of the possibility that its Bt protein, Cry9C, may be a human allergen. This protein had been modified to slow its digestion and prolong its effect in the insect gut and this change rendered the protein less digestible in the human gut as well. With the exception of Cry9C, none of the new proteins in foods evaluated through the FDA consultation process has the characteristics of an allergen. There is currently no evidence that the health of any consumer has been affected by exposure to StarLink corn (CDC, 2001) or any other BD food.

The only documented case where a human allergen was introduced into a food component by genetic engineering occurred when attempts were made to improve the nutritional quality of soybeans using a Brazil nut protein, the methionine-rich 2S albumin. Allergies to the Brazil nut have been documented (Arshad *et al.*, 1991), and while still in pre-commercial development, testing of these new soybeans for allergenicity was conducted in university and industrial laboratories. It was found that serum from people allergic to Brazil nuts also reacted to the new soybean (Nordlee *et al.*, 1996). Once this was discovered, further development of the new soybean variety was halted and it was never marketed. This work led to the identification of the major protein associated with Brazil nut allergy which was previously unknown (Nordlee *et al.*, 1996).

### 3. Will insertion of the transgene increase the potential hazard from toxins or pharmacologically active substances present in the host?

Concern has been expressed about the randomness with which genes are inserted into the host by current genetic engineering processes. This could (and does) result in 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 (Conner and Jacobs, 1999).

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 by their effects on the development, growth or fertility of the host or by the extensive testing of its chemical composition compared to isogenic untransformed plants that is typically conducted.

Over 5000 field trials with more than 70 different transgenic plant species have been conducted since 1987 in the United States by the USDA Animal and Plant Health Inspection Service (APHIS). In only one instance has an unexpected result been seen. In

this case a mutation in a color gene and gene silencing through changes in the methylation status of these genes led to unexpected color patterns in petunia flowers. Both of these effects are also seen in conventional plant breeding (Meyer *et al.*, 1992). While the possibility of an undetected increase in a toxic component in a new food cannot be entirely eliminated, the current safeguards make this quite unlikely and no toxicologically or nutritionally significant changes of this type are evident in the transgenic plants so far marketed for food production.

A frequently-quoted example of the dangers of genetic engineering relates to the production of the amino acid, tryptophan, used as a dietary supplement. After genetic engineering of the microorganisms used in this fermentation, a number of cases of eosinophilia-myalgia syndrome (EMS) were reported among users of the supplement. However, prior to these cases, the manufacturing process was also changed and certain filtration and purification steps were removed. Although the cause of the outbreak has, regrettably, never been clarified, and the nature of the toxic impurity remains a matter of conjecture, it appears much more likely that the changes in the manufacturing process rather than genetic modifications in the microorganism were to blame (Mayeno and Gleich, 1994).

These examples indicate that careful analysis of the changes in BD organisms is necessary to ensure against unexpected alterations in the levels of toxins, allergens and essential nutrients. This will be particularly critical if, as seems likely, engineering of the synthetic pathways of secondary metabolites is undertaken in plants e.g. to increase their resistance to insects and pathogens or produce compounds of pharmaceutical value. Such changes might create new and unanticipated secondary compounds with unknown toxic properties.

#### 4. Does the possible transfer of antibiotic resistance marker genes from the ingested BD food to gut microbes present a significant human hazard?

Organisms that contain DNA encoding for antibiotic resistance proteins are common and of increasing prevalence in the environment. However, a contribution of the antibiotic resistance markers in BD foods to antibiotic resistance in gut bacteria has not been documented and, for several reasons including efficient destruction of the resistance gene in the human gut and the extremely low intrinsic rate of plant-microbe gene transfer, it is expected to be extremely small (Royal Society, 1998). In any case, such resistance genes occur quite widely already and the antibiotics involved are not widely used in medical practice (Nawaz *et al.*, 2001). Finally, the technology is now available to omit the use of such selection devices (e.g. Goldsbrough *et al.* 1996; Koprek *et al.* 2000) and their use is likely to diminish.

#### 5. Will genetic transformation adversely affect the nutritional value of the host?

In the USA, the FDA is entrusted with assuring that the nutritional composition of BD foods is substantially equivalent to that of the non-modified food. Studies are performed to determine whether nutrients, vitamins and minerals in the new food occur at the same

level as in the conventionally-bred food sources (e.g. see Berberich *et al.* (1996) and Sidhu *et al.* (2000)). A typical example is the case of Roundup Ready soybeans. In this case, the protein, oil, fiber, ash, carbohydrates and moisture content and the amino acid and fatty acid composition in seeds and toasted soybean meal were compared to conventional soybeans. Fatty acid compositions and protein or amino acid levels of soybean oil were compared and special attention was given to checking the levels of antinutrients typically found in soybeans, e.g., trypsin inhibitors, lectins and isoflavones (Padgett *et al.*, 1996). The only difference between the conventional and non-conventional soybeans was detected in defatted, non-toasted soybean meal, the starting material for commercially utilized soybean protein. In this form, trypsin inhibitor levels were 11 - 26% higher in transgenic soybeans. The levels of the trypsin inhibitors were similar in all lines in the seeds and in defatted, toasted soybean meal, the form used in foods. The results of this study demonstrated that, except for the trypsin inhibitors in non-toasted soybean meal, which is not consumed, the composition of transgenic lines is equivalent to that of conventional soybean cultivars. In addition, the equivalence of the feeding value of these transgenic grains was demonstrated in rats, chickens, catfish and dairy cattle (Hammond *et al.*, 1996).

#### 6. Will the transgene product adversely affect non-target organisms?

In addition to the general concerns addressed under food safety, additional attention is needed when the gene product is pesticidal or otherwise may be toxic to non-target organisms that consume it. The effects of each transgene product that is designed for pesticidal effects must be evaluated on a case-by-case basis against target and non-target organisms under specific field growth conditions for each transgenic crop. The foremost current example of this is the incorporation of Bt genes into crop plants for insect control. The toxic properties of Bt endotoxins to both target and non-target species of many kinds are well known (Betz *et al.*, 2000). They show a narrow range of toxicity limited to specific groups of insects, primarily Lepidoptera, Coleoptera or Diptera, depending on the Bt strain. Nevertheless, Bt-producing plants have been tested broadly to determine whether any alteration in this limited spectrum of toxicity has occurred, without the discovery of any unexpected results (see Orr and Landis (1997), Pilcher *et al.*, (1997), and Lozzia *et al.* (1998) for examples of such studies). Exotoxins and enterotoxins, which are much more broadly toxic than the endotoxins, are also produced by some Bt strains, but these are not present in the transformed plant.

In plants transformed with Bt genes to control lepidopterans, toxicity to non-target lepidopterans would be expected if exposure occurs by feeding on the transformed crop. A long and contentious debate has ensued over the potential toxicity of the Bt toxin in corn pollen to the Monarch butterfly after initial laboratory studies showed increased mortality in larvae (Losey *et al.*, 1999). It is unlikely that a substantial risk to these butterflies exists in the field (e.g. see Sears *et al.*, 2001), but the details of this controversy are beyond the scope of this article. Beyond the question of the potential toxicity of Bt corn to such valued insects, it is also important to recollect that the common alternative is to spray corn with insecticides, which are not as selective as Bt toxin.

## Future Challenges in the Assessment of the Safety of BD Foods

Current safety assessment methodologies are focused primarily on the evaluation of the toxicity of single chemicals. Food is a complex mixture of many chemicals. Using animal models, the evaluation of most aspects of the safety of single components of the diet, such as a Bt toxin, is possible using widely accepted protocols. Future projects may involve more complicated manipulations of plant chemistry. In this case, safety testing will be more challenging. Whole foods cannot be tested with the high dose strategy currently used for single chemicals to increase the sensitivity in detecting toxic endpoints (MacKenzie, 1999; Royal Society of Canada, 2001). Also, the question of potential deleterious interactions between new, or enhanced levels of known, toxic agents in BD foods will undoubtedly be raised. The safety-testing of multiple combinations of chemicals remains a difficult proposition for toxicologists. In view of these challenges, there is a clear need for the development of effective protocols to allow the assessment of the safety of whole foods (NRC, 2000; Royal Society of Canada, 2001),

## Conclusions

1. The responsibility of toxicologists is to assess whether foods derived through biotechnology are at least as safe as their conventional counterparts and to ascertain that any levels of additional risk are clearly defined. In achieving this, it is important to recognize that it is the food product itself, rather than the process through which it is made that should be the focus of attention. In assessing safety, the use of the substantial equivalency concept provides guidance as to the nature of any new hazards.
2. There is no reason to suppose that the process of BD food production leads to hazards of a different nature than those already familiar to toxicologists. The safety of current BD foods compared to their conventional counterparts can be assessed with reasonable certainty using established and accepted methods of analytical, nutritional and toxicological research.
3. A significant limitation may occur in the future if transgenic technology results in more substantial and complex changes in a foodstuff. Toxicologists are currently limited in their ability to assess the hazard presented by complex mixtures, and have not yet developed methods by which whole foods (as compared to single chemical components) can be fully evaluated for safety. Progress also needs to be made in developing definitive methods for the identification and characterization of protein allergens and this is currently a major focus of research.
4. The level of safety of current BD foods to consumers appears to be equivalent to that of traditional foods. Verified records of adverse health effects are absent although the current passive reporting system would probably not detect minor or rare adverse effects. However, this is no guarantee that all future genetic modifications will have such apparently benign and predictable results. A continuing evolution of toxicological methodologies and regulatory strategies will be necessary to ensure that this level of safety is maintained.

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