The Safety of Genetically Modified 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 current consensus 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.

The available scientific evidence indicates that the potential adverse health effects arising from biotechnology-derived foods are not different in nature from those created by conventional breeding practices for plant, animal, or microbial enhancement, and are already familiar to toxicologists. It is therefore important to recognize that the food product itself, rather than the process through which it is made, should be the focus of attention in assessing safety.

We support the use of the substantial equivalence concept as part of the safety assessment of biotechnology-derived foods. This process establishes whether the new plant or animal is significantly different from comparable, nonengineered plants or animals used to produce food that is generally considered to be safe for consumers. It provides critical guidance as to the nature of any increased health hazards in the new food. To establish substantial equivalence, extensive comparative studies of the chemical composition, nutritional quality, and levels of potentially toxic components, in both the engineered and conventional crop and animal, are conducted. Notable differences between the existing and new organism would require further evaluation to determine whether the engineered form presents a higher level of risk. Through this approach, the safety of current biotechnology-derived foods can be compared with that of their conventional counterparts, using established and accepted methods of analytical, nutritional, and toxicological research.

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. At present, no verifiable evidence of adverse health effects of BD foods has been reported, although the current passive reporting system probably would not detect minor or rare adverse effects or a moderate increase in effects with a high background incidence such as diarrhea.

The changes in the composition of existing foods produced through biotechnology are quite limited. Assessing safety may be more difficult in the future if genetic engineering projects cause more substantial and complex changes in a foodstuff. Methods have not yet been developed with which whole foods (in contrast 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. Improved methods of profiling plant and microbial metabolites, proteins and gene expression may be helpful in detecting unexpected changes in BD organisms and in establishing substantial equivalence.

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 current consensus position on the safety of foods produced through biotechnology. In this context, biotechnology is taken to mean those processes whereby genes that are not endogenous to the organism (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 co-
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. We do not consider here some aspects of the possible environmental impact of GM organisms such as gene transfer to nonengineered plants.

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 in plants have included resistance to antibiotics (kanamycin/neomycin or ampicillin) or herbicides.

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 overexpression 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.

The Concept of Substantial Equivalence

The guiding principle in the evaluation of BD foods by regulatory agencies in Europe and the U.S. 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; Kuiper et al., 2001; Maryanski, 1995; OECD, 1993) 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, 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 nonequivalent, which would mean that more extensive safety testing might be necessary. The examination of substantial equivalence, therefore, may be only 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 meaning of “substantial” and how equivalency should be established, and debate over its use continues (e.g., see Millstone et al., 1999 and following correspondence; Kuiper et al., 2001; Royal Society of Canada, 2001), the concept appears to be logical and robust in assessing the safety of foods derived from both genetically modified plants and microorganisms (FAO/WHO, 2000, 2001a). If it can be established with reasonable certainty that a BD food is no less safe 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. A recent study of FDA procedures for assessing the safety of BD foods by the U.S. General Accounting Office reviews these procedures and concludes that the current regimen of safety tests are adequate to assess existing BD foods (U.S. General Accounting Office, 2002).

Key Issues with Respect to Human Health Effects of BD Foods

Is the Transgene Itself Toxic? Can it be Transferred to the Genome of a Consumer?

Humans typically consume a minimum of 0.1 to 1 gram of DNA in their diet each day (Doerfler, 2000). 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 as 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, 2000). Although much remains to be learned about the fate of dietary DNA in mammalian systems (Doerfler, 2000), the possibility of adverse effects arising from the presence of transgenic DNA in foods, either by direct toxicity or gene transfer, is minimal (FAO/WHO, 2000; Royal Society, 2002).

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.

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 the U.S. EPA (1998, 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; Kuiper et al., 2001; Siegel, 2001). In this case, 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 safety evaluations. However, each new transgenic product must be considered individually, based on exposure levels and its potency in causing any toxic effects, as is typical of current risk assessment paradigms for chemical agents.

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 markets in the 1960s 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 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?

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 was published in 1996 (Metcalfe 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, 2001b). The main approaches currently used in the evaluation of allergenicity are:

- 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 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.
- 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. In these cases, other approaches such as structural homology searches and the use of animal models may be effective in identifying potential new allergens.
- Use of animal models. Currently there are no widely accepted or thoroughly evaluated animal models available 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 U.S. 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. After the accidental introduction of StarLink corn into the human food chain, a limited number of illnesses among consumers were reported. These were investigated by the Centers for Disease Control, who found no evidence that the corn products were responsible (CDC, 2001). However, although this study is reassuring, methodological limitations make it less than conclusive (Kuiper et al., 2001), and it cannot eliminate the possibility that some adverse effects may have occurred that were not reported. Because of this incident, StarLink corn is no longer marketed. With the exception of Cry9C, none of the engineered proteins in foods so far evaluated through the FDA consultation process has had the characteristics of an allergen.

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 precommercial 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).

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).

Unexpected and potentially undesirable pleiotropic or mutagenic changes in the genome of the host do occur (e.g., see a recent listing by Kuiper et al., 2001), but these would likely be revealed by their effects on the development, growth, or fertility of the host, or by the extensive testing of its chemical composition compared with isogenic untransformed plants, which is a necessary part of any safety evaluation of transgenic crops.

In the U.S., since 1987, the USDA Animal and Plant Health Inspection Service has completed over 5000 field trials with more than 70 different transgenic plant species. The only unexpected result was a mutation in a color gene and gene silencing through changes in the methylation status of these genes that 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 unlikely, and no toxicologically or nutritionally significant changes of this type are evident in the transgenic plants so far marketed for food production.

Substantial public concern about the safety of BD products was raised in 1989 when a number of cases of eosinophilia-myalgia syndrome (EMS) were reported among users of the amino acid tryptophan as a dietary supplement. By mid-1993, 37 deaths had been attributed to this outbreak (Mayeno and Gleich, 1994). The development of the syndrome appeared among users of some batches of the supplement after a change in the manufacturing process that included the use of a new genetically modified microorganism in the fermentation. However, concomitant with this change were additional alterations in certain filtration and purification steps used previously in the manufacturing process. The exact cause of the outbreak and the nature of the toxic impurity have not been established with certainty. Thus, it is not possible to determine whether the change in purification, the genetic engineering of the organism, or some other factor or factors were to blame (Mayeno and Gleich, 1994). A subsequent investigation revealed that cases of EMS also occurred among consumers of tryptophan before the GM organism was introduced into the manufacturing process, although at a lower incidence. Thus, the genetic modifications might have caused an increase in the level of the agent that was responsible for tryptophan-associated EMS, but it did not create a novel toxicant (Sullivan et al., 1996). This event is troubling in that the tryptophan would be regarded as highly purified (99.6% or higher), and no adequate animal model has been found to replicate EMS, a probable autoimmune disease.
This illustrates that toxicology has limits in its ability to explain and predict adverse effects in humans.

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 analysis 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 to produce compounds of pharmaceutical value. Such changes might create new and unanticipated secondary compounds with unknown toxic properties. New approaches to profiling changes in metabolites, proteins, and gene expression (Kuiper et al., 2001) may be helpful in such cases.

Does the Possible Transfer of Antibiotic Resistance Marker Genes from the Ingested BD Food to Gut Microbes Present a Significant Human Hazard?

The development of antibiotic resistance among pathogenic bacteria is a significant human health issue. However, no contribution to antibiotic resistance in gut bacteria arising from antibiotic resistance markers in BD foods has been documented. For several reasons, including the efficient destruction of the resistance gene in the human gut and the very low intrinsic rate of plant–microbe gene transfer, any contribution from this source is expected to be extremely small (Royal Society, 1998). Genes for resistance to kanamycin and related antibiotics already occur quite commonly in the environment, including in the flora of the human gut, which naturally contains about 1 trillion \(10^{12}\) kanamycin- or neomycin-resistant bacteria (Flavell et al., 1992). Even if the occasional transfer of resistance from plant to bacterium did occur, the practical impact would be negligible. However, since any increase in antibiotic resistance is recognized as undesirable and the technology is now available to omit the use of such marker genes, future genetically modified organisms are unlikely to contain them (e.g., see Goldsbrough et al., 1996; Koprek et al., 2000). Thus, concerns related to their use are likely to diminish.

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 nonmodified 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; 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 with 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 (Padgette et al., 1996).

One difference between the conventional and nonconventional soybeans was detected in defatted, nontoasted soybean meal, the starting material for commercially utilized soybean protein, which is not itself consumed. In this material, trypsin inhibitor levels were 11–26% higher in the 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. Except for this difference in trypsin inhibitor levels, all other nutritional aspects were equivalent between the transgenic line and the conventional soybean cultivars. Feeding studies demonstrated that there were no evident differences in nutritional value between the conventional and transgenic soybeans in rats, chickens, catfish, and dairy cattle (Hammond et al., 1996). Domestic animal feeding studies with a number of other transgenic crops (e.g., see Kuiper et al., 2001) have similarly shown no significant adverse changes in nutritional value.

Will the Transgene Product Adversely Affect Nontarget Organisms?

In addition to the general concerns addressed that relate to food safety, additional attention is needed when the gene product is pesticidal or otherwise may be toxic to nontarget 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 nontarget 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 nontarget 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 Gatehouse et al., 2002; Lozzia et al., 1998; Orr and Landis, 1997; and Pilcher et al., 1997 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, because their genes are not transferred into the crop.

In plants transformed with Bt genes to control lepidopterans, toxicity to nontarget lepidopterans would be expected if exposure occurs by feeding on the transformed crop. Particular concern has been expressed over the potential toxicity of the Bt toxin in corn pollen to the Monarch butterfly after initial laboratory studies showed increased mortality in larvae fed on leaves dusted with transgenic pollen (Losey et al., 1999). However, most transgenic corn pollen contains much lower nonlethal levels of Bt toxins than the strain used in this study,
and there is only a limited synchrony between the feeding period of the most sensitive younger larvae and the period when corn pollen is shed. Also, corn pollen does not typically move far beyond the borders of the field, leaving significant amounts of milkweed uncontaminated in many locations. For these reasons, a detailed risk assessment concluded it is unlikely that a substantial risk to these butterflies exists in the field since only a negligible portion of the population is exposed to toxic levels of Bt (Gatehouse et al., 2002; Sears et al., 2001). 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 synthetic insecticides, which are not as selective as the Bt toxin. In a sweet corn field containing milkweed plants and treated with a synthetic pyrethroid for insect control, 91–100% of the monarch butterfly larvae placed on the milkweed leaves after spraying were killed. In plots where Bt sweet corn was planted and the pollen fell naturally on the milkweed leaves, larval death rates were much lower (7–20%) and indistinguishable from those in untreated non-Bt corn plots (Stanley-Horn et al., 2001).

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

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 goal, 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.

Scientific analysis indicates that the process of BD food production is unlikely to lead to hazards of a different nature from those already familiar to toxicologists. The safety of current BD foods, compared with their conventional counterparts, can be assessed with reasonable certainty using established and accepted methods of analytical, nutritional, and toxicological research.

A significant limitation may occur in the future if transgenic technology results in more substantial and complex changes in a foodstuff. Methods have not yet been developed by which whole foods (as compared with 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. Improved methods of profiling plant and microbial metabolites, proteins, and gene expression may be helpful in detecting unexpected changes in BD organisms and in establishing substantial equivalence.

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, nor can it detect a moderate increase in common effects such as diarrhea. 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.

REFERENCES


Kimber, I., and Dearman, R. J. (2001). Can animal models predict food allergenicity? 


