Review

Food Safety Evaluation of Crops Produced through Biotechnology

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Agricultural biotechnology has been widely adopted in agriculture but is also the focus of controversy. Questions have arisen regarding food and environmental safety. In the US, responsibility for ensuring agricultural and environmental safety is delegated to the USDA and EPA, respectively. The FDA has primary responsibility for food safety, with the exception that the EPA has responsibility for the safety of proteins in plants associated with insect defense mechanisms. The food safety assessment, whether performed by the FDA or the EPA, requires evaluation of the safety of 1) the newly added DNA, 2) the safety of the newly introduced gene product and 3) the overall safety of the balance of the food. A paradigm called "Substantial Equivalence" guides the assessment. The principal food safety issues for new varieties crops are 1) potential toxicity of the newly introduced protein(s), 2) potential changes in allergenicity, 3) changes in nutrient composition, 4) unintended effects giving rise to allergenicity or toxicity and 5) the safety of antibiotic resistance marker-encoded proteins included with the transgene. All of these must be taken in the context of the predicted range of dietary exposures. The evaluation seeks to establish that there is a "reasonable likelihood of safety" and that new varieties are as safe as or safer than crops produced by traditional methods. Indeed, after extensive safety testing and some five years of experience with such crops in the marketplace, there is not a single report that would lead an expert food scientist to question the safety of such transgenic crops now in use.

Key teaching points:

- The EPA, USDA and FDA have responsibility for regulating the food and environmental safety of food produced through biotechnology.
- Substantial Equivalence guides the identification of differences between a new variety and its conventional counterpart.
- Pre-market safety assessment evaluates the safety of the newly introduced DNA and proteins. Predicted dietary exposure is an important consideration.
- A major focus of the assessment is to determine if any unintended and undesirable changes have occurred. Similarity of the plant's appearance, properties and composition is evidence that no significant changes have occurred.
- The crops approved to date (50) are essentially identical to their conventional counterparts.
- The safety assessment has concluded that there are no new or unusual risks and that the crops are as safe as their conventional counterparts.

INTRODUCTION

If one regularly watches the news on TV or reads a newspaper it would be difficult not to have noticed the controversy surrounding the introduction of agricultural biotechnology in recent years. The biotechnology industry and research scientists have claimed these new crops provide benefits to consumers, producers and the environment. The potential of the technology to improve nutritional value and promote food security for the hungry has been emphasized. US regulatory agencies have approved 50 applications of biotechnology to the development of new plant varieties in the US.

Numerous food and environmental advocacy groups have expressed concerns about crops developed via biotechnology

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because they view these crops as distinctly new and different organisms that are being injected into our food supply. Consumers are doubtless confused about who and what to believe concerning this new technology and these new varieties. One point of view among some consumers, probably more in Europe than in the United States, is that these foods are extremely dangerous. Activist critics call them "Frankenfoods." These critics have carried out an active media campaign designed to frighten consumers, and this has caused some grocery stores and restaurants to guarantee their customers that their products are free of "genetically modified" foods. This is, of course, very difficult to do in the US since 70% to 85% of all processed/packaged foods contain one or more ingredients that are ultimately derived from what their detractors call "genetically modified organisms" or GMOs. This is largely due to the fact that biotechnology is the most rapidly adopted technology in the history of agriculture; approximately 70% of the soybeans and 25% of the corn planted in the US this year came from biotechnology-derived seeds. At the same time, there can be little doubt that some consumers are sincerely concerned because they fear that biotechnology is unsafe and that products developed via biotechnology are so different than conventional foods that they should be avoided.

BACKGROUND

What Do We Really Know about Food Biotechnology?

One of the challenges offered by the critics of biotechnology is that there is little known about the safety of these foods. It is sometimes claimed that *no* research has been done. A major objective of this review is to describe the scientific and regulatory evaluation process that is applied to a new crop variety derived through biotechnology before it is approved for cultivation and introduction into the market place. There is an extensive amount of in-depth information about this topic available in print and via the internet. Far too much information is available, in fact, to include in a brief review. Many of the references appended to this review are themselves reviews that contain extensive bibliographies the reader can access the research literature. Each of the regulatory agencies, (i.e., EPA, FDA and USDA) that are involved in the approval process have posted extensive background information on their websites. The Institute for Food Technologists has published an Expert Report on Biotechnology and Food that can be obtained in print or can be down-loaded from a website (http://www.ift.org/govtrelations/biotech/). A recent comprehensive review of the food safety evaluation by Kuiper *et al.* has been published in the *The Plant Journal* [1]. A website that contains a variety of databases such as a searchable bibliography as well as background materials on virtually every aspect of biotechnology is available (http://www.agbios.com). Materials can be downloaded directly or requested in the form of a free CD-ROM.

Is Biotechnology New and Different?

The scientists who develop them would like to believe that what is most "different" about these products is that every new variety is unique and each provides unique kinds of solutions to agricultural challenges. Detractors would say that any use of this technology is dangerous. The traditional regulatory approach that we have used to protect the safety of our food and preserve our environment does not accept that *all* biotechnology is bad or dangerous simply because it is new or different. It asserts, instead, that biotechnology is a new tool and technologies aren't, in and of themselves, good or bad. How you use the technology, how you apply it, can be appropriate or inappropriate, good or bad, costly or risky or beneficial. We need to determine if each potential new product or plant variety will be a useful, beneficial and safe development. Past history has shown that we often don't categorically accept or reject a technology until we have accumulated a number of years of experience with its application. Had we not taken a "wait and see" approach, we would have given up on railroads after the first couple of years of passenger rail in the United States because early train travel was very unsafe and often lethal. We also would have given up on electricity early on because there were many fires, injuries and deaths from electricity until we learned how to apply the technology correctly. A major lesson here is that we should analyze and judge the safety of *individual products* that are the applications of a new technology rather than the technology itself. Put another way, it is the safety of the product, not the safety of the technology used to create it that should be the focus of safety evaluation.

Modern agriculture evolved through a long history of genetic manipulation of plants to improve their agronomic and nutritional value. One has only to look at the striking difference between modern corn and its grass-like ancestor, teosinte, to understand the dramatic genetic chances that have resulted from millennia of plant breeding. There are few varieties of fruits and vegetables consumed today that bear much resemblance to their wild ancestors. In spite of the striking genetic differences that have been introduced into crops, there is a long history of successfully evaluating the safety of such crops. In general, with but a handful of exceptions, we have found that new foods produced through plant breeding are safe to consume. The standard embodied in the regulatory approval process is that there must be a reasonable certainty that no harm will occur from the introduction of a novel food or ingredient. It was the opinion of the US National Academy of Science [2, 3] and the National Research Council [4] that biotechnology posed no new or unusual risks. More importantly, any new risks should be of the same kinds as those that are associated with crops produced by conventional genetic breeding. It is an important underlying principle of the safety evaluation that

these crops present no new or different risks. In effect, it would justify the application of the safety paradigm used for conventional foods to be applied to crops produced through biotechnology.

How Is Biotechnology Regulated?

Although the science indicated that no new or different risks were present, new more rigorous regulatory processes are used to assess the food, feed, and environmental safety of crops developed via biotechnology. Regulators, scientists and the industry choose to err on the side of precaution. It is ironic, then, that critics challenge that a more precautionary approach should be taken. There are several excellent websites that describe the regulatory processes in detail [5]. There are nine steps in the United States in the regulatory process [5]:

1. Biosafety Committee—NIH Biosafety Guidelines
2. USDA greenhouse approval
3. USDA field trial authorization
4. USDA authorization transport for field trials
5. USDA permission to commercialize
6. EPA experimental use permit approval
7. EPA determination of food tolerance or tolerance exemption
8. EPA product registration
9. FDA review process

It takes seven to ten years to navigate the regulatory waters, and, in the US, three government agencies—the USDA, EPA and FDA—are involved. There are several public hearings, and there is some opportunity for public input into the process. Opportunity for public input, transparency of process and availability of information could, however, be improved so that there could be no misunderstanding about the nature of the regulatory process. A recent Issues Paper on the regulatory approval process has been published by CAST [5] and is available in hard copy or as a downloadable PDF.

This review will specifically focus on the scientific evaluation underlying Step 9, the FDA's food safety review [6]. There is one exception to the FDA authority to regulate the food safety of biotechnology-derived crops. The EPA has responsibility for the food safety of the bacterial proteins present in insect-protected products such as Bt corn. These insect toxic proteins were once called plant pesticides, but are now classified as plant protectants. The same strategy and principles are used by both agencies, since both are confronted with essentially the same food safety considerations.

This review will also introduce the concept of Substantial Equivalence (SE) as it is applied to the food safety evaluation [7]. The SE concept states that, since it is difficult to compare the safety of whole foods, differences in safety can be determined by evaluating the safety issues associated with the established differences between two foods. As will be seen in subsequent sections, adoption of this strategy results in a heavy reliance on compositional analysis and a focus on the newly introduced traits since that is often the only measurable difference from the conventional comparator. The reliance on compositional analysis and the term "Substantial Equivalence" have been interpreted by some critics to mean that regulators are reaching the conclusion that food is safe merely because it is found to be "substantially equivalent." They further complain that this is a flawed and circular conclusion when two varieties are in fact different. The important point is that SE, the departure point for a safety evaluation paradigm that *begins* with a comparison, is intended to discern differences meriting further investigation [7].

DESCRIPTION OF SUBJECT

What are the Food Safety Issues?

According to guidance provided by government regulators, pre-market food safety evaluation should consider the issues listed below [6, 9].

1. Safety of the source organism and gene(s)
   a. Safety of the inserted DNA
   b. Safety of DNA Ingestion
   c. Safety of the antibiotic resistance marker (if used)
2. The food safety issues of the newly introduced product(s)
   a. Potential for Toxicity (protein product)
   b. Potential for Allergenicity (protein product)
   c. Safety of any unintended effects
3. Equivalence of Composition
4. Retention of Nutritional Value
5. The human dietary exposure

The "Safety of the Source Organism" is considered first. One might assume that a gene or genes that are derived from a commonly eaten food crop would not provoke the same degree of scrutiny as would the use of genes from a highly toxic source. In practice, the degree of scrutiny is the same. Risk is minimized if the gene products intended for introduction have been characterized and their function and metabolic fate established. It is a given that they should not encode toxicants, anti-nutrients or other potentially physiologically hazardous activities.

There are few safety issues associated with the ingestion of the newly introduced DNA *per se*. There exist no reported incidents in which DNA has been shown to be toxic. Despite fears and claims to the contrary, there are also no known instances of plant-derived DNA being taken up and incorporated into the mammalian genome [8]. Dietary DNA is usually degraded when consumed and is quickly hydrolyzed and digested to nucleotides in the human GI tract [8].

Antibiotic resistance markers (ARM) are used to help identify the transformed plants after the transformation (DNA introducing process). Plants that have incorporated the new DNA, including the ARM, will grow in culture that contains the antibiotic. Transformed cells containing the desired newly

introduced genes can then be selected for further study. Concerns have been raised about the safety of using antibiotic resistance markers in crops developed through biotechnology. Some fear that ARM genes will transfer to bacteria in the soil and gut and give rise to increased levels of antibiotic resistance. Transfer of plant DNA to bacteria has never been observed in nature, nor has it been possible to demonstrate transfer laboratory experiments. More importantly and unfortunately, antibiotic resistance genes are already widespread in nature. Kanamycin resistance, a marker that is often used in biotechnology, is often present in 10% or more of bacteria randomly isolated from soil. Misuse and poor stewardship of antibiotics in animal agriculture, veterinary and human medicine may have led to the widespread dissemination of ARM genes in nature. There is certainly cause for concern about the indiscriminate use of antibiotics that has led to this situation, but plants containing ARM genes are highly unlikely to contribute to the problem. Banning the use of ARM genes in biotechnology is unlikely to improve the situation [7]. To address these concerns, biotechnologists are developing alternative selection systems that do not utilize ARM genes.

New genes are incorporated into transformed plants in order to confer new desirable traits on the plants. Almost without exception, these traits are the result of the transcription and translation of the genes to synthesize newly acquired proteins in the plant. Toxicological evaluation is routinely performed on purified preparations of the recombinant protein(s) that have been newly introduced. The toxicological evaluation typically answers the following questions:

What Is the Anticipated Human Dietary Exposure?

Data taken from national food consumption surveys can be used to predict the dietary exposure of consumers to the new variety or the proteins that it contains. The data is typically sorted into groups of special nutritional interest such as by age, gender and pregnant or lactating women. Other demographic factors such as ethnicity are considered as well. This evaluation can be complex since ingredients derived from commodities such as corn and soybeans can be found in a large variety of food products. The biotechnology-derived crop is seldom eaten as such; it is usually processed into ingredients and/or incorporated in formulated processed food products. The evaluation of Bt-corn will be used here as an example [10, 11]. The plant-protecting proteins in Bt are referred to as "Cry" proteins. Cry is an abbreviation for the "crystalline" proteins found in *Bacillus thuringiensis* spores that are toxic to a specific narrow range of insects. Approximately 1% of the whole corn used for food in the US is consumed in products such as tortillas and corn chips, while the balance is milled and fractionated into food ingredients such as starch and corn oil.

In late 2000, FDA recalled foods that contained, or might contain, StarLink corn. StarLink corn had been approved by the EPA for use as animal feed, but had not yet been approved for use in human foods. It was found that StarLink corn had become inadvertently intermingled with corn destined for food processors. DNA from StarLink was detected in taco shells and other whole-corn containing products. Data on human exposure to Cry9c, the Bt protein that was in StarLink corn, provide a useful example. Since StarLink corn was only 0.4% of the US corn crop, only very small amounts entered the human food chain [12]. The dietary exposure to Cry9c by 99th percentile consumers of corn products (Table 1) was predicted to be less than 1 μg/day of Cry9c. The table breaks out the data for Hispanics, since it was thought that their higher consumption of dry-milled corn in the form of tortillas and other whole corn products might lead to higher levels of StarLink consumption. This appears not to have been the case. This author is unaware of any reported toxin that is potent enough to cause a biological effect at these predicted 99th percentile levels of exposure. The policy of zero-tolerance for unapproved ingredients and additives justified the recall by FDA. Nonetheless, numerous reports of adverse effects were attributed to the consumption of Cry9C tainted products. The CDC has been unable to determine if Starlink consumption was the cause any of these incidents or that any of the adverse effects were related to allergic reactions to Cry9C [13].

Table 1. Predicted Human Dietary Exposure to Cry9C: 99th Percentile Consumers

Group Selected	Cry9C Protein Consumed μg/day	Total Protein from Corn μg/day	Total Protein All Foods μg/day
US Population	0.37	9,752,000	219,600,000
Children 1–6 yrs	0.25	6,183,000	125,900,000
US Hispanic	0.21	16,261,000	209,500,000
US Hispanic Children 1–6 yrs	0.15	6,818,000	130,200,000

The dietary exposure to the Cry proteins from human food-approved Bt crops that are in the marketplace today is estimated to be in the range of 1–10 μg/day if all corn were Bt-corn. By comparison, the daily consumption of protein is usually between 100–300 million μg/day [12]. In this context, exposure to new proteins in products developed via biotechnology is very low.

Does the Protein Cause Observable Adverse Effects When Feed at Dietary Levels Is Far in Excess of Those Anticipated to Occur in the Human Diet?

Experimental animals are fed doses in the range of 1 to 5 mg/kg/day [9, 11]. The studies can be evaluations of acute toxicity lasting no more than a few days or weeks, or evaluations of chronic toxicity, with studies lasting for three months to a full life cycle.

None of the Cry proteins thus far evaluated has produced any adverse effect at any level of administration to animals. As will be seen in the next section, this is likely due to their rapid

digestibility. Compared to an estimated human exposure of about 1 μg/kg/day, this represents a *five millionfold safety factor*. In contrast, the toxicological standard routinely used in food safety evaluations is that there should be no observable effect at dietary levels only *a hundredfold higher* than those that would occur in the diet.

Is the Protein Digested in the Human GI Tract?

In vitro digestibility studies using simulated gastric fluid reveals that the Cry proteins in all of the Bt-corn products thus far approved for human consumption is digested by gastric fluid in approximately 30 seconds [9, 11]. The Cry9C protein present in Starlink corn, however, appears to be more stable to digestion. At low pH values (fasted state), it is digested in 30 minutes, while at higher pH values (feeding) the protein is somewhat more stable [9]. It is thought that proteins that are quickly digested would be unable to exert significant biological activity. If a protein such as Cry9C is not rapidly degraded, it could in principle retain biological activity (see the discussion of Cry9C and allergenicity below).

Is the Protein Destroyed by Food Processing?

Food processing operations such as thermal preservation, dry-milling or wet-milling often degrade and denature proteins giving rise to loss of their biological activity. The Cry proteins found in approved Bt-corn varieties are easily degraded by food-processing operations [9, 11]. In contrast, Cry9C appears somewhat more stable to processing, although it has been established that it is destroyed by wet-milling [13]. The partial destruction by food processing of Cry9C makes it unlike the other Cry proteins that are totally denatured and broken down by thermal processing. From a toxicological point of view, Cry proteins present very little hazard due to their large margin of safety and the fact that they are readily degraded.

Is the Protein Potentially a Food Allergen?

Food allergies affect 6% to 8% of children and 1% to 2% of adults. Ingestion of an allergen against which a person has become sensitized can produce symptoms as mild as oral irritation or minor gastric discomfort, or—albeit infrequently—as severe as anaphylactic shock followed by death. Some of the most common foods in our diet can cause allergy: corn, eggs, soy, rice, wheat, brazil nuts, peanuts, seafood, crustaceans and milk. Most food allergens are proteins, often major protein components of the offending food. Repeated ingestion of large amounts of the proteins is usually necessary for sensitization to occur. Food allergens typically are resistant, or at least partially resistant, to digestion and food processing. Food allergy is a complex and rapidly evolving field that has received increased attention in recent years [14]. More research is needed, however, in at least three general areas: 1) the nature of the human food allergic response, 2) an understanding of the structure(s) and sequences that lead to allergencity that is robust enough to allow predictions of allergencity to be made and 3) the development of a validated animal model with which allergencity can be predicted.

The safety assessment seeks to ensure that new allergens will not be introduced into foods in which consumers would not previously have expected them to occur. Fig. 1 is a flow chart for assessing the potential allergenicity of a product developed through biotechnology [7]. If a gene is isolated from a food that is known to cause food allergies, such as nuts, the path on the left side of the flowchart is followed. IgE-containing sera isolated from allergy sufferers can be used to directly assay allergenicity of the new food. A negative reaction can be followed by a confirmatory skin-prick test. Negative skin-prick reactions can be confirmed through double-blind placebo controlled food challenge protocols. Since sera can be isolated from allergic subjects, a definitive evaluation can be made for proteins isolated from foods containing known allergens. To ensure safety, however, developers of biotech crops avoid taking genes from plants known to contain allergenic proteins.

The pathway described in the right hand portion of Fig. 1 is applied to foods containing novel proteins with no history of consumption and/or no history of food allergencity. If a protein does not resemble known allergens at the level of protein sequence and structure and it is readily digested and/or destroyed by food processing, there is a reasonable likelihood that it will not provoke new food allergies. However, if a protein resists gastric digestion for 30 minutes, as was the case with Cry9c, it is difficult to conclude that it is not allergenic. There is no definitive evidence that Cry9c *is* an allergen, but since it displays partial resistance to digestion, the possibility that it *could* be a food allergen can not be eliminated. In the absence of proof that Cry9c was not an allergen, Starlink was not approved by the EPA for food use.

Have Unintended Changes Occurred in the Plant Breeding Process?

The most obvious unintended change that might occur is an alteration of composition or nutritional content. Extensive chemical, biochemical and nutritional analyses are performed on each new variety. Proximate analysis, amino acid analysis, protein profiles, carbohydrate analysis, lipid analysis, fatty acid analysis, vitamin and mineral content are usually determined. In addition, known anti-nutrient or potentially health beneficial compounds which might be important are assayed as well [9, 10, 11]. For example, changes in isoflavone or trypsin inhibitor content in soybeans would be evaluated. In some cases, the concentration of hundreds of cellular metabolites has been determined. A large amount of data has been accumulated on new varieties. The results are easily summarized. No significant differences in composition or nutrient content have been observed in the crop varieties approved to date. Animal feeding studies have been performed in order to determine if the new

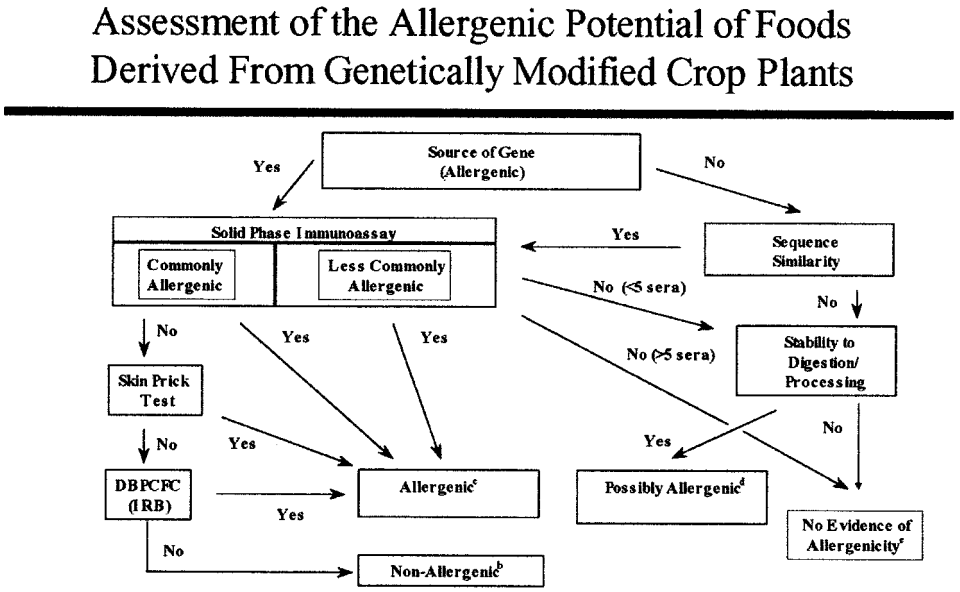

Fig. 1. Flow chart for the assessment of potential allergencity of crops derived through biotechnology [7]. The series of steps used to assess the allergenicity of proteins isolated from plants that contain known allergens flows down the left side of the chart. The abbreviation DBPCFC in the box in the lower left corner stands for double-blind placebo-controlled food challenge. The protocol must be approved by an Human Subjects Institutional Review Board (IRB). The pathway down the right side of the figure shows the steps that are used to evaluate potential allergenicity of a protein isolated from a plant not known to cause food allergy.

varieties give similar feed performance to conventional varieties [16]. No differences have been noted between biotechnology-derived and conventional feeds [16]. The animal studies reinforce the conclusion that these varieties have essentially the same nutritional value.

The Substantial Equivalence paradigm focuses attention on any safety issues associated with differences between a novel food and its most appropriate comparator. If no significant compositional differences are observed, SE directs primary attention to the safety of the newly introduced protein as described in the preceding sections. Perhaps it should not be too surprising that plant varieties which have been bred and selected to resemble their conventional counterparts in every detail of growth, hardiness, yield, appearance, size and a host of other agronomic parameters should be identical in composition. It is also reassuring that analysis demonstrates that hundreds of intracellular metabolites are present at identical concentrations as are found in conventional counterparts. Given the highly interconnected and interdependent nature of biochemical pathways in the cell and the tightly coupled regulatory processes that govern the concentration of intermediates and fluxes through metabolic pathways, it is highly unlikely that major changes in specific metabolite concentrations have gone unnoticed. It is impossible to rule out the possibility, however, that the concentration of one or more minor secondary metabolites differs in two varieties of the same plant.

It should also be noted that compositional changes are not *per se* a safety concern. One can imagine many compositional changes that would enhance safety such as reduction or elimination of an anti-nutrient. Other changes, such as increases in ω-3 fatty acids, β-carotene or Vitamin E, could be health beneficial.

Unintended changes are not new to the food supply. They occur frequently in conventional plant breeding. In fact, the generation of compositional changes, such as enhancing monounsaturated fatty acid content in soybeans or Lysine in corn has sometimes been the objective of plant breeding. There is no reason to suppose that small changes do not occur when biotechnology is applied. No two varieties of the same plant species are identical in composition; representatives of the same variety grown in different locations, soils, climates or years often will have significantly different compositions. It will never be possible to conclude that a product developed via biotechnology, or any other technology, is 100% safe because it is impossible to prove there were no unintended changes in some minor but previously undetected or unappreciated component. The question pursued in the food safety assessment is this: "If any unintended changes did occur, is there any reason to believe these changes would raise more of a safety concern than changes that could and do arise from new crops developed via conventional breeding?"

CONCLUSIONS

The objective of pre-market regulatory review of crops produced through biotechnology is to ensure food safety for

consumers. The preceding sections have briefly outlined the steps used by regulatory agencies in the pre-market safety assessment. The reader must of course decide for himself or herself whether the evaluation described above is sufficiently rigorous to ensure food safety. The National Academy of Science of the US and several other countries, OECD, FAO, WHO and numerous international agencies have been joined by dozens of scientific societies and the overwhelming majority of scientists in stating that after years of study and safe use there is no evidence of harm or unusual risk associated with this technology [5]. Crops produced through biotechnology have proven to be *as safe as or safer than* crops produced by conventional breeding.

How could these crops be *safer*? Less pesticide is used on Bt-corn. This reduces pesticide exposure to farm workers, to the communities surrounding farms and ultimately to consumers. It also lessens the impact of agricultural pesticides on non-target insects such as the monarch butterfly. Labor and energy are saved as farmers go into their fields with heavy equipment less often. More importantly, Bt-corn is significantly safer for human consumption than conventional corn because it contains two- to twentyfold lower concentrations of highly toxic mycotoxins [11]. Fewer corn kernels are injured by corn borers when Bt-corn is grown, leading to less opportunity for mycotoxin-producing molds to develop.

One cannot deny that agricultural biotechnology has been the subject of much controversy. Critics of the technology are convinced that biotechnology poses food safety threats. These imagined dangers have much more impact on consumers when they are reported in the media than do reports of advancements and successes such as those mentioned in the preceding paragraph. It is quite normal for consumers to pay more attention to possible dangers in their food than they do to agricultural successes. Food selection is a complex process that can be greatly influenced by doubts about safety, wholesomeness or quality.

There are a variety of complex reasons—ethical, political, social, economic, trade-related—for opposition to biotechnology. In this author's opinion, fears about food safety are greatly exaggerated by critics and are unsupported by science. The following example illustrates the phenomenon. Scottish researchers Ewen and Pusztai reported to British media in 1999 that feeding genetically engineered potatoes containing a gene encoding a Snowdrop lectin caused "proliferative and antiproliferative" changes in the GI epithelial cells in rats. They concluded the effects were due to the "genetically modified" nature of the potato and not the toxicity of the lectin *per se*. After rejection at peer-reviewed journals, *Lancet* published a paper describing this work so that the data would be publicly available [17]. Perhaps unfortunately, the article is now cited by critics of biotechnology as scientific evidence that genetic modification *per se* creates safety problems. And they can point to the reputable scientific journal in which these findings have been published. After studying the evidence and listening to testimony, a British Royal Society commission reported that no scientifically meaningful conclusion could be reached from Ewen and Pusztai's experiments [18]. The commission noted in part, that the animals were fed large quantities of raw potatoes which are toxic to rodents (and humans), the experimental diets were protein deficient, the diets were supplemented during the experiments, the experiments were terminated prematurely, the comparator potato was not isogenic and the number of animals in the experiment was too small for a statistically significant conclusion to be drawn.

My purpose here is not to make a one-sided argument for the safety of foods and food ingredients derived through biotechnology, but rather to make a plea for sound science to prevail over alarmism and emotionalism. Ensuring food safety for the consumer should be the primary objective. Prepared scientific minds should always be alert and vigilant for signs of harm or negative effects. There is no such thing as zero risk in the food supply. It would be foolish to claim foods produced through biotechnology present zero risk to consumers. The objective is to produce crops that present no new, different or unusual risks and to keep the risks within reasonably acceptable limits. Those who are opposed to the technology for reasons outside the scope of food safety would quickly respond that they will accept zero risk from a technology and an industry that they oppose.

The widespread need for improved nutrition education is well known to readers of this journal. Improved science literacy in general is needed if consumers are to make informed decisions about biotechnology. My concern is that, if we do not effectively explain the science, consumers will have no other basis upon which to decide than that which opponents and critics have dramatically presented to them. There is also the possibility that the controversy over biotechnology will divert our focus from more important food safety and nutrition issues. Whatever hypothetical but unrealized risks might be associated with biotechnology, there exist far greater and more certain risks in the food system. Food borne illness and improper diet are associated with significant morbidity and mortality in this country and around the globe.

From High Risk to Low Risk:

Food borne illness*
Diet: sufficiency, adequacy, overnutrition*
Untested natural foods and dietary supplements
Natural toxicants*
Food allergy*
Chance additives
Pesticide and herbicide residues*
Food ingredients and additives*
GMO foods*

*Biotechnology can be part of the solution.

The above list places food-related health issues in descending order of importance. An asterisk has been placed on those issues for which biotechnology may be useful in developing solutions. Removing the toxicants, anti-nutrients or allergens from a foodstuff is an example of how biotechnology could be used to improve food safety and public health.

Even if the food safety issues are resolved in favor of agricultural biotechnology, as I have suggested can be done, controversy will remain because there are many facets to the critics' arguments against biotechnology. Perhaps in the coming years the controversy over biotechnology can be converted to a meaningful dialog about a variety of important global social and political issues that remain unresolved. Better still, perhaps it will lead to a more science-literate consumer who makes wiser diet choices. It is hoped that this brief review will help some turn their attention to more pressing issues and enable them to explain to others how food safety is ensured by our government agencies.

REFERENCES

1. Kuiper HA, Kleter GA, Noteborn HPJM, Kok EJ: Assessment of the food safety issues related to genetically modified foods. Plant J 27:503–528, 2001.
2. National Academy of Sciences: "Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues." Washington, DC: National Academy Press, 1987.
3. National Academy of Sciences: "Genetically Modified Pest-Protected Plants: Science and Regulation." Washington, DC: National Academy Press, 2000.
4. NRC National Research Council: "Field Testing Genetically Modified Organisms: Framework for Decisions." Washington, DC: National Academy Press, 1989.
5. Council For Agricultural Science and Technology (CAST): "Evaluation of the U.S. Regulatory Process for Crops Developed through Biotechnology." Washington, DC: CAST, 2001.
6. Food and Drug Administration: Statement of policy: Foods derived from new plant varieties. Federal Register 57: 22984, 1991.
7. FAO/WHO: Safety Aspects of Genetically Modified Foods of Plant Origin. Report of a Joint FAO/WHO Expert Consultation on Foods Derived from Biotechnology. World Health Organization (WHO), in collaboration with the FAO (Food & Agriculture Organization of the United Nations). WHO Headquarters, Geneva, Switzerland, May 29–June 2, 2000. http://www.fao.org/es/esn/gm/biotec-e.htm (Website accessed February 1, 2002).
8. Beever DE, Kemp CF: Safety issues associated with the DNA in animal feed derived from genetically modified crops. A review of scientific and regulatory procedures. Nutr Abs Rev 70:175–182, 2000.
9. Chassy B: Food safety assessment of current and future plant biotechnology products. In Thomas J, Fuchs R (eds): "Biotechnology and Safety Assessment," 3rd ed. San Diego: Academic Press, in press.
10. Astwood J, Fuchs RL: Status and safety of biotech crops. ACS Symposium Series 774. Agrochem Discovery Insect Weed Fungal Control 14:152–164, 2001.
11. Betz FS, Hammond BG, Fuchs RL: Safety and advantages of *Bacillus thuringiensis*-protected plants to control insect pests. Regul Toxicol Pharmacol 32:156–173, 2000.
12. Petersen BJ, Rachman NJ, Watters JL: "Estimated Potential Dietary Intake of Cry9c Protein Based on Measurements of Cry9c in Processed Foods Made from 100% Starlink." Report to EPA, April 12, 2001. http://www.epa.gov/pesticides/biopesticides/otherdocs/stlink/stlinkdata.htm (Website accessed February 1, 2002).
13. Investigation of Human Health Effects Associated with Potential Exposure to Genetically Modified Corn. http://www.cdc.gov/nceh/ehhe/Cry9cReport/recommendations.htm (Website accessed February 1, 2002).
14. Aventis Crop Science. Detection of Cry9C Protein in Dry Milled, Wet Milled and Masa Processed Fractions and Processed Foods Made From 100% StarLink Grain. April 17, 2001. http://www.epa.gov/pesticides/biopesticides/otherdocs/stlink/stlinkdata.htm (Website accessed February 1, 2002).
15. Joint FAO/WHO Expert Consultation on Foods Derived from Biotechnology—Allergenicity of Genetically Modified Foods. World Health Organization (WHO), in collaboration with the Food & Agriculture Organization of the United Nations (FAO)—Rome, January, 22–25, 2001. http://www.fao.org/es/esn/gm/biotec-e.htm (Website accessed February 1, 2002).
16. Clark JH, Ipharraguerre IR: Livestock performance: feeding biotech crops. J Dairy Sci 84(E. Suppl.): E9–E18, 2001.
17. Ewen SWB, Pusztai A: Effect of diet containing genetically modified potatoes expressing *Galanthus nivalis* lectin on rat small intestine. Lancet 354:1353–1354, 1999.
18. Royal Society: Review of Data on Possible Toxicity of GM Potatoes (Ref. 11/99). London: The Royal Society, (Website accessed on February 1, 2002). http://www.royalsoc.ac.uk/templates/statements/statementDetails.cfm?StatementID=29.

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