Food Safety and Quality: Assessing the Impact of Biotechnology

Ian C. **Munro**
Director
Canadian Centre
for Toxicology
645 Gordon St.
Guelph, Ontario
N1G 1Y3
and
Richard L. Hall
President
International Food
Biotechnology
Council
7004 Wellington Ct.
Baltimore, MD 21212

Reay Tannahill (1973), in her fascinating *booh Food in History*, points out that the safety and quality of foods has been a concern of humankind since primitive times. Concerns over food safety and quality magnified substantially along with the development of the food trade, due to the widespread practice of food adulteration employed by earlier food purveyors. It is interesting to note historically that the legislation these practices prompted form the basis for the development of modern food control legislation. But concerns over food safety today extend beyond the question of adulteration which, as we all know, is infrequently practiced by today's food merchants. In terms of their scientific importance, microbiological safety of foods is the predominant concern, followed by nutritional factors, natural toxicants, industrial pollutants, and finally, pesticides and food additives. The emerging science of biotechnology and the impact it will have on food safety and quality is added to these traditional areas of food safety concern.

To grasp the potential food safety and regulatory issues that might occur pursuant to the introduction of biotechnology into the food and agriculture industry, it is necessary to understand the nature of the issues being dealt with. An industry survey conducted in 1988 by the Food and Drug Administration (FDA, 1988) indicated that about 40 percent of the research and development in food biotechnology was focused on improved agricultural products, 43 percent was targeted at the food processing industry and the balance, approximately 20 percent, was targeted in the area of food safety diagnostics and related applications. The

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research and development programs in agriculture were evenly divided between livestock biotechnology, the bioengineering of pest resistance into food crops and the development of improved cultivars. In the food processing industry, two-thirds of the activity was focused on new or improved food ingredients while the balance was targeted on food processing techniques such as enzyme technology and improved final products. The important point here is not the quantitative distribution of resources, but the fact that biotechnology holds great promise for application in essentially all sectors of the agricultural and food processing industry.

Given this breadth of application, what will the major scientific issues associated with the application of biotechnology to the food system be? Certainly the principal concern is one of food safety. A second concern relates to the possible impact biotechnology will have on the nutrient composition of the food supply. From a government perspective, the regulatory issues that will undoubtedly be associated with biotechnology cannot be overlooked. These range from *if* and *how* biotechnology food products should be regulated, i.e., "Will specific product approvals be required?", to the whole question of regulatory compliance procedures, including analytical requirements, labeling etc. The impact biotechnology will have on food safety has been evaluated by the International Food Biotechnology Council (IFBC, 1990) and some of these remarks are based on the recently completed IFBC report.

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It is important to consider the legal framework in which we have to operate in any consideration of the effect of biotechnology on food safety. The overriding objective of current food safety laws is, of course, to assure that consumers are not harmed by the foods they eat. To achieve this objective, the law provides an array of safety standards and enforcement tools which the FDA can use to control foods that are potentially harmful to health. A key premise of the law is that safety standards and regulatory procedures should be tailored to the nature of the food substance in question and the potential safety questions it may pose.

Whole foods are not required to undergo any pre-market review or approval by FDA. Under the law, however, any person who introduces food into commerce is responsible for assuring that it complies with all require-

ments of the Food, Drug and Cosmetic Act, including the requirement that it meet the applicable safety standards. The FDA has enforcement powers under the statute that permit it to seize adulterated food, seek a court order preventing its further distribution, and criminally prosecute firms and individuals responsible for its distribution.

The law also recognizes that the food supply contains many naturally-occurring substances that, when consumed alone in large amounts, are toxic, but that are not harmful when consumed as inherent constituents of food. The FDA is empowered to act against such substances if it finds that they render the food "ordinarily injurious" to health.

Substances added intentionally to accomplish a function in food are subject to yet another safety standard, and may be required to undergo pre-market review and approval by FDA. Even here, however, the intent is to foster innovation in food technology, as well as assure safety. These goals are achieved by adopting a protective but realistic safety standard and by not requiring pre-market approval when safety assurance is not required, for example, when the food substance is "generally recognized as safe" (GRAS). As FDA has interpreted and applied the law over the years, formal pre-market approval has generally been reserved for new chemicals and new uses of chemicals that are not GRAS. The FDA has also developed special procedures and practices for the regulation of GRAS substances.

Clearly, the extent of regulatory concern, as well as safety and nutritional components, will vary depending upon the food product or ingredient of biotechnology being considered. To deal with the easy problems first, a regulatory structure already exists to ensure the safety of ingredients such as food additives and GRAS substances. It is fairly clear that new ingredients and even old ingredients produced through biotechnology will be required to meet present regulatory requirements. This covers the bulk of enzymes, microorganisms, food additives such as thickening agents and preservatives as well as GRAS food ingredients such as specific sources of dietary fiber, modified carbohydrates, etc. Collectively, this represents a vast array of substances used by the food processing industry. Except for specific examples, there is really nothing new about these groups of substances. Humans have used microorganisms to "process" foods for centuries, albeit it is only recently that controlled fermentations have been commonplace. Likewise, food additives and other ingredients have enjoyed widespread legitimate use and are now well integrated into the technology of the food processor. The existing regulatory practices will apply to all such products. That does not mean that each new product will require for-

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mal review by FDA. In many cases, new products will be considered GRAS substances. In a great many other cases, biotechnology is simply a convenient, cost-efficient way to produce existing, already approved food ingredients. To comment on the safety issues associated with biotechnology in the food processing industry, it can be safely stated that existing procedures for safety evaluation and regulatory control will effectively eliminate any potential risks that may be perceived to exist.

The primary issue in food biotechnology relates to its application in agriculture. The real or perceived issues associated with bovine somatotropin are now familiar, along with other emerging problems associated with the genetic manipulation of food-producing animals. Less well recognized, and probably less well understood, are the issues that relate to the application of biotechnology in the plant kingdom. Again, the regulatory and food safety issues differ depending on the application and the end product in question. Two general categories of application can be envisioned. One of these relates to the use of biotechnology to produce herbicide, insect, drought and other forms of plant resistance by engineering foreign genetic material into the plant, while a second category relates more to altering the traditional characteristics of existing cultivars by the insertion of genetic material derived from traditional food sources. These latter changes might include alterations in composition; for example, improved nutritional quality or improved processing characteristics, and increased yield and marketability. In future years the development of new varieties of cultivars, at least new to our palate, might be anticipated.

A record of regulatory experience existing in plants does not yet exist in the safety evaluation of plants or genetic variants of existing plants. Yet a great deal of human experience is available—in fact, many generations of experience in the area of traditional plant breeding techniques. The key to dealing with the problem of biotechnology as applied to plants lies in large part, in the historical experience and the safety record of human use on past practices which exists but is not well documented. The experience of that record provides an important foundation for the safety evaluation of genetically-modified plants.

Primitive humans soon learned which plants were poisonous and should not be eaten and which were not. Yet even today, several poisonous plants are consumed of necessity and are stored, processed or prepared in

such a way as to alter or eliminate their toxicity. A typical example is the root plant cassava which, once properly processed, provides a wholly suitable and nutritious basic food staple for large segments of the world's population. Many other such examples exist, including soybeans, lima beans and even potatoes. Prudent and judicious selection of foods derived from a broad selection of plant fauna available to early humans provided the genetic stock for the plant foods eaten today.

The introduction of plant breeding brought with it not only changes in genetic elements, but vast improvements in the food supply. The genetic lineage of modern cultivars is lost in antiquity, but a perspective on the genetic variations people have historically been exposed to provides an example of the genetic diversity inherent in the present food supply. One of the world's staple foods—maize—probably originated from the wild grass teosinte commonly found in remote areas of Mexico and Central America. Selection and cultivation changed teosinte into Indian corn and finally into modern maize. Unquestionably, humans have been exposed to a wide array of genetic variants of today's maize without apparent adverse health effects over time. The extent of change with time of the genetic diversity in the food supply becomes evident when the differences between cultivated plants and their wild relatives is considered. Cultivated plants usually have one or more of the following traits that are uncommon in their wild relatives: lessened ability to disseminate seed, reduced concentrations of bitter or toxic principles, loss of delayed germination attribute, reduced life span, higher harvest index or altered color and fruit size. This illustrates the point that *we and our ancestors have been exposed to wide diversity of genetic material.* This becomes important in assessing the impact of biotechnology on food safety.

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The extent of compositional variation inherent in the foods traditionally eaten is another factor to consider in assessing the safety of genetically-modified foods. Some of this variation is due to genetic differences, while some is due to environmental influences. Among the macronutrients present in commercial vegetables, intraspecies variations in protein, fat and carbohydrate content range from 1.5-2.5 fold. Similar variations are present in common commercial fruit varieties. Among essential trace elements within species, variations in composition of up to 10 fold are not uncommon. The intraspecies content of some trace elements such as sele-

nium may vary up to 18 fold while vitamin content varies up to approximately 4 fold. While not immediately apparent, these are very wide variations in composition. An example illustrates: if a variety of carrots that contains the higher of the range of vitamin A traditionally present is consumed, all daily vitamin A needs from that source would essentially be met. But if a variety low in vitamin A is consumed, only 25 percent of the daily requirement would be met. This highlights the importance of understanding the impact of biotechnology on the nutrient composition of foods.

A third, and probably the most important factor to consider in determining the consequences of genetic manipulation of plants, is the *affect* it has on the concentration of naturally-occurring toxic factors. This is a principal concern of regulatory agencies, even while recognizing that traditional plant breeding practices have been used to advantage to reduce levels of toxic constituents. In the early 1970s, FDA cited six incidents which raised questions of safety regarding traditional plant breeding and which brought these practices under the purview of GRAS regulations. These included:

—a 60 percent increase in solanine content of potatoes grown from seed tubers treated with 1,000 rads of gamma radiation to break dormancy;

—the development of a high solids potato cultivar with high solanine content;

—the hypothesis that potatoes resistant to late blight developed additional chemicals that are teratogenic;

—the production of the toxic chemical ipomeamarone by sweet potatoes under certain environmental conditions;

—the development of cultivars of food plants resistant to insect attack;

—unexpected changes in plant composition due to other varietal changes (the example given was reduced vitamin C in tomatoes due to mechanical harvesting).

The FDA indicated that an increase in toxicants of 10 percent or more when compared to the parent containing the least toxicant, or a decrease in a principal nutrient of 20 percent or more, would require that appropriate analytical data be supplied to FDA in a GRAS affirmation petition.

Despite plant breeder's concern over FDA regulation the vast majority of new plant varieties have not been formally reviewed under GRAS regulations and have not required pre-market approval from the FDA. Nonetheless, we must be vigilant to the possibility that biotechnology may introduce new toxic factors into plants or alter the levels of existing toxicants.

There are now over 200 naturally-occurring toxic factors in food that have some potential for causing toxic effects in humans, although only 21 have been firmly documented as causing human harm. These include both toxic factors in food plants and in animal feeds and forage where the toxicant is passed on to human food such as milk. These are important for the plant breeder to consider because:

—Selection and traditional breeding practices have been among the most successful methods used to reduce concentrations of natural toxicants to levels that present no significant hazard;

—Natural toxicants will clearly be the principal point of concern in evaluating the safety of foods produced by genetic modification of sources in which these toxicants can occur;

—It should certainly be the intent of any genetic modification to reduce, or at least maintain the level of any constituent that even approaches being a significant hazard;

—Natural toxicants are an important, and, within professional circles, a well-recognized source of risk in food.

As with nutrients, genetic variations may markedly alter the toxicant content of foods. For example, the solanine content of white table potatoes may vary from 2 to a high of 20 mg / 100 g, a ten-fold variation. The higher level could represent 20 percent of the toxic dose of solanine to humans. In fact, during the 1970s, the U.S. Department of Agriculture (USDA) developed a potato variety (Lenape) with unusually high solids content and, therefore, desirable processing characteristics. This variety also derived late blight resistance from a wild ancestor, *Solarium demissum*. In the course of routine monitoring of incoming potatoes for glycoalkaloid (solanine) content, a food company found solanine levels several times higher than normal in the Lenape variety. The company called the problem to the attention of USDA and FDA and the variety was quickly withdrawn. Similarly, low cyanogen varieties of cassava yield 20 - 40 mg / kg of hydrogen cyanide while other varieties may yield 20 times that amount—enough to poison a person who is not aware of the proper processing procedures.

The examples quoted are clearly well known, but the potential for genetic modification to alter the levels of less well known toxicants must never be overlooked. As recently as 1981, Rymal *et al* (1984) reported that as the result of quality control testing, a large commercial pack of tomato sauce containing squash was kept out of commerce because the squash was found to be extremely bitter. Samples of the fruit of this cultivar were found to contain unusually high levels of the extremely toxic substance

Cucurbitacin E. This episode, as well as others where people were actually poisoned from home garden crops in Alabama and Australia, apparently resulted from a "wide cross" contamination of the cultivated seed from a wild relative.

Criteria for Assessing Safety and Acceptability

This provides the background to attempt to elaborate on the criteria that are important in assessing the safety and acceptability of genetically-modified food crops. If the process of genetic modification is intended to introduce new genetic elements that result in a wholly new expression product, for example, a resistance factor such as a pesticide derived through enzymatic means, then clearly we should in theory, identify and characterize the substance, its range of levels of occurrence and conduct a safety evaluation on it as a discrete entity if possible. If it is not possible to isolate the substance, it may be necessary to evaluate the safety of the whole food.

If the genetic change is intended to enhance the nutritional quality of a food, then documentation supporting the achieved objective would be required. If the genetic change was intended to enhance processing characteristics, yield or marketability, this would likewise need to be demonstrated. In all cases, a critical feature of the safety evaluation would consist of characterizing the nature of the introduced genetic material, particularly if it is not from a traditional food source. The following should be known about the inserted genetic material:

—the physical and functional limits of the coding region, and size and structure;

—the physical extent of the signal DNA regions;

—the functional properties of signals such as promoters where the sequence, relative strength and start of transcription are known from published literature or direct determinations.

—after the genetic material is introduced and an individual genetically-modified plant has been selected, the following additional information may be obtained: quantitative data on the levels and consistency of the expression products from the introduced gene.

—copy number of the introduced gene and vector sequences.

—documentation concerning the concentration of significant nutrients in the product. Significant nutrients are defined as those that contribute in a major way to achieving recommended daily intakes. Other nutrients, though important, would not be critical to gaining acceptance of the product.

Documenting the levels of any known naturally-occurring toxic factors inherent in the plant species or its close relatives. This would involve analytical determinations of the precise levels of those naturally-occurring toxic factors in the food on which attention should focus.

If deemed necessary, documenting that genetic manipulation has not altered the physical and elemental composition of the food in such a way as to impinge on the microbiological safety of the food when processed in accordance with usual practices.

In practice, it is important to revise these criteria in light of the principle that the standard of safety for biotechnologically-produced foods should be no more or no less stringent than that required for food produced through conventional breeding techniques. What can be concluded about the impact of biotechnology on food safety? It can be stated safely that food ingredients and additives produced through biotechnology will not be a new issue to the science of food safety because of the well established safety evaluation practices that exist for these classes of substances.

With respect to whole foods such as genetically-modified plants, the extent of safety evaluation will need to be geared to the nature of the induced genetic change. Given the specificity of modern techniques in molecular biology, as applied to biotechnology, changes in genetic composition hopefully could be characterized with greater ease and more precision than in the past. The genetic alterations induced through genetic engineering probably would not be as extensive as those induced through traditional breeding practices, especially wide crosses.This tends to limit the extent of compositional change that might occur. The degree of government regulatory oversight required will depend on the degree of technical excellence the industry demonstrates. The reward for adequately characterizing introduced genetic material, and providing other data referred to will be reduced time to approval in cases where premarket approval is required. The penalty for failing to do so will be increased regulatory scrutiny consisting of repeated requests for more data, more complete explanations, and, worst of all, requests to test the new product in extensive animal feeding trials. This is to be avoided in the name of good science.

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References

FDA, (1988) *Food Biotechnology: Present and Future,* Food and Drug Administration, Rockville, MD.

IFBC, (1990) *Biotechnologies and Food: Assuring the Safety of Foods Produced by Genetic Modification,* International Food Biotechnology Council, Washington, DC.

Rymal, K.S., O.L. Chambliss, M.D. Bond. (1984) Squash containing toxic cucurbitacin compounds occurring in California and Alabama USA, *J. Food Prot.*, 47, 270-271.

Tannahill, R. (1973) *Food in History,* Stein and Day, New York.