❑ UNDERSTANDING BIOTECHNOLOGY IN AGRICULTURE

By Lester M. Crawford, Deputy Commissioner, U.S. Food and Drug Administration

Bioengineering provides distinct advantages over traditional breeding technologies because the risk of introducing detrimental traits is likely to be reduced, says Deputy U.S. Food and Drug Administration Commissioner Lester Crawford. Crawford, a doctor of veterinary medicine by training, argues that there are no scientific reasons that a product should include a label indicating that it, or its ingredients, was produced using bioengineering. He also outlines draft guidelines to strengthen controls that would prevent biotech products in field trials from inadvertently getting into food or feed.

Based on two decades of experience with bioengineered foods and overwhelming scientific data that these foods are safe to eat, we believe that biotechnology can offer a safe and important tool for both exporting and food-deficit countries. This paper describes some of the basic science behind biotechnology, the U.S. regulatory structure for ensuring safe foods and U.S. policy on the issue of labeling.

CROSS-BREEDING, HYBRIDIZATION AND BIOENGINEERING

Scientists have been improving plants by changing their genetic makeup since the late 1800s. Typically, this has been accomplished through cross-breeding and hybridization, in which two related plants are cross-fertilized and the resulting offspring have characteristics of both parent plants. In the breeding process, however, many undesirable traits often can appear in addition to the desirable ones. Some of those undesirable traits can be eliminated through additional breeding, which is time consuming. Breeders can then further select and reproduce the offspring that have the desired traits. Many of the foods that are already common in our diet are obtained from plant varieties that were developed using conventional genetic techniques of breeding and selection. Hybrid maize, nectarines, which are genetically altered peaches, and tangelos, which are a genetic hybrid of a tangerine and grapefruit, are all examples of such breeding and selection.

Today, by inserting one or more genes into a plant, scientists are able to produce a plant with new, advantageous characteristics. The new gene splicing techniques are being used to achieve many of the same goals and improvements that plant breeders historically have sought through conventional methods. They give scientists the ability to isolate genes and introduce new traits into foods without simultaneously introducing undesirable traits. This is an important improvement over traditional breeding. Because of the increased precision offered by the bioengineered methods, the risk of introducing detrimental traits is actually likely to be reduced.

FOOD SAFETY CONCERNS

The U.S. Food and Drug Administration (FDA) has found no evidence to indicate that either ordinary plant deoxyribonucleic acid (DNA) or the DNA inserted into plants using bioengineering presents food safety problems. Nor are the small amounts of the newly expressed proteins likely to change dramatically the safety profile of the plant. If safety concerns should arise, however, they would most likely fall into one of three broad categories: allergens, toxins or anti-nutrients. FDA has extensive experience in evaluating the safety of such substances in food. It is important to note that the kinds of food safety testing typically conducted by developers of a bioengineered food crop to ensure their foods meet all applicable requirements of the Food, Drug and Cosmetics Act (FD&C Act) address these potential concerns. In the event that something unexpected does occur, this testing provides a way to detect such changes at the developmental stage and defer marketing until any concern is resolved.

As aforementioned, some of the food safety concerns that could arise include:

Allergens: Foods normally contain many thousands of different proteins. While the majority of proteins do not cause allergic reactions, virtually all known human allergens are proteins. Since genetic engineering can introduce a new protein into a food plant, it is possible

that this technique could introduce a previously unknown allergen into the food supply or could introduce a known allergen into a "new" food.

Toxins: It is possible that a new protein, as introduced into a crop as a result of the genetic modification, could cause toxicity.

Anti-nutrients: It is possible that the introduction of anti-nutrients, such as molecules like phytic acid, could reduce essential dietary minerals such as phosphorus.

The use of genetic engineering techniques could also result in unintended alterations in the amounts of substances normally found in a food, such as a reduction of Vitamin C or an increase in the concentration of a naturally occurring toxicant in the plant food.

LEGAL AND REGULATORY ISSUES

One important component in ensuring food safety is the U.S. regulatory structure. The FDA regulates bioengineered plant food in conjunction with the United States Department of Agriculture (USDA) and the Environmental Protection Agency (EPA). FDA has authority under the FD&C Act to ensure the safety of all domestic and imported foods for man or animals in the United States market. The exceptions to this are meat, poultry and certain egg products, which are regulated by USDA. The safety of animal drug residues in meat and poultry, however, is regulated by FDA. Pesticides, including those bioengineered into a food crop, are regulated primarily by EPA. USDA's Animal and Plant Health Inspection Service (APHIS) oversees the agricultural and environmental safety of planting and field testing bioengineered plants.

Bioengineered foods and food ingredients must adhere to the same standards of safety under the FD&C Act that apply to their conventionally bred counterparts. This means that these products must be as safe as the traditional foods in the market. FDA has the power to remove a food from the market or sanction those marketing the food if the food poses a risk to public health. It is important to note that the FD&C Act places a legal duty on developers to ensure that the foods they market to consumers are safe and comply with all legal requirements.

FOOD ADDITIVES

A substance that is intentionally added to food is a food additive, unless the substance is generally recognized as safe (GRAS) or is otherwise exempt, such as a pesticide whose safety is overseen by EPA. The FD&C Act requires premarket approval of any food additive regardless of the technique used to add it to food. Thus, substances introduced into food are either new food additives that require premarket approval by FDA, or GRAS and are therefore exempt from the requirement for premarket review. Generally, foods such as fruits, vegetables and grains are not subject to premarket approval because they have been safely consumed over many years. Other than the food additive system, there are no premarket approval requirements for foods generally.

Under FDA policy, a substance that would be a food additive if it were added during traditional food manufacturing is also treated as a food additive if it is introduced into food through bioengineering of a food crop. Our authority permits us to require premarket approval of any food additive and, thus, to require premarket approval of any substance intentionally introduced via bioengineering that is not generally recognized as safe.

Examples of substances intentionally introduced into food that would be reviewed as food additives include those that have unusual chemical functions, have unknown toxicity, or would be new major dietary components of the food. For example, a novel sweetener bioengineered into food would likely require premarket approval. In our experience with bioengineered food to date, however, we have reviewed only one substance under the food additive provisions, an enzyme produced by an antibiotic resistance gene, and we granted it approval as a food additive. In general, substances intentionally added to or modified in food via biotechnology to date have been proteins and fats that are, with respect to safety, similar to other proteins and fats that are commonly and safely consumed in the diet and, thus, are presumptively GRAS. Therefore, they have not needed to go through the food additive approval process.

PRE-MARKET CONSULTATIONS

FDA has established a consultative process to help companies comply with the FD&C Act's requirements for bioengineered foods that they intend to market. The

results of our consultations are public information and are available on our website at: http://www.cfsan.fda.gov/~lrd/biocon.html. Since the consultation process was created, companies have used the process more than 50 times as they sought to introduce genetically altered plants representing more than 10 different crops into the U.S. market. We are not aware of any bioengineered plant food that is subject to FDA's jurisdiction and is on the market that has not been evaluated by FDA through the current consultation process.

Typically, the consultation begins early in the product development stage, before the product is ready for market. Company scientists and other officials meet with FDA scientists to describe the product they are developing. The agency then advises the company on what tests would be appropriate for the company to assess the safety of the new food. After the studies are completed, the data and information on the safety and nutritional assessment are provided to FDA for review. FDA evaluates the information for all of the known hazards and also for potential unintended effects on plant composition and nutritional properties since plants may undergo changes other than those intended by the breeders. For example, FDA scientists are looking to assure that the newly expressed compounds are safe for food consumption and that there are no allergens new to the food, no increased levels of natural toxicants, and no reduction of important nutrients. They are also looking to see whether the food has been changed in any substantive way such that the food would need to be specially labeled to reveal the nature of the change to consumers.

If a plant developer used a gene from a source whose food is commonly allergenic, FDA would presume that the modified food might be allergenic. The developer, however, is allowed the opportunity to demonstrate that such food would not cause allergic reactions in persons allergic to food from the source.

Our experience has been that no bioengineered product has gone on the market until FDA's questions about the safety of the product have been answered.

LABELING

One of the most important issues confronting the biotechnology industry is that of labeling. Under the FD&C Act, a food is misbranded if its labeling is false or misleading in any particular way.

FDA does not require labeling to indicate whether or not a food or food ingredient is a bioengineered product, just as it does not require labeling to indicate which conventional breeding technique was used in developing a food plant. However, if genetic modifications materially change the composition of a food product, these changes must be reflected in the food's labeling. This would include its nutritional content (for example, more oleic acid or greater amino acid or lysine content) or requirements for storage, preparation or cooking, which might impact the food's safety characteristics or nutritional qualities. For example, one soybean variety was modified to alter the levels of oleic acid in the beans. Because the oil from this soybean is significantly different from conventional soybean oil, we advised the company to adopt a new name for that oil, a name that reflects the intended change.

If a bioengineered food were to contain an allergen not previously found in that food and if FDA determined that labeling would be sufficient to enable the food to be safely marketed, FDA would require that the food be labeled to indicate the presence of the allergen.

FDA has received comments suggesting that foods developed through modern biotechnology should bear a label informing consumers that the food was produced using bioengineering. We have given careful consideration to these comments. However, we do not have data or other information to form a basis for concluding that the fact that a food or its ingredients were produced using bioengineering constitutes information that must be disclosed as part of a bioengineered product's labeling. Hence, we believe that we have neither a scientific nor a legal basis to require such labeling. We have developed, however, draft guidance for those who wish voluntarily to label either the presence or absence of bioengineered food in food products.

STRENGTHENING CONTROLS OVER FIELD TRIALS

In August 2002, President Bush's Office of Science and Technology Policy (OSTP) proposed strengthening controls over field trials to address the potential of material from field trials inadvertently getting into food or feed.

FDA's task is to publish draft guidance for comment on procedures to address the possible intermittent, low-level presence in food and feed of new non-pesticidal proteins

from biotechnology-derived crops that are under development for food or feed use but have not gone through FDA's premarket consultation process. Under this guidance, FDA would encourage sponsors, domestic and foreign, to submit protein safety information when field testing showed that there could be concerns that new non-pesticidal proteins produced in the field-tested plants might be found in food or feed. FDA's focus would be on proteins new to such plants because FDA believes that at the low levels expected from such material, any food or feed safety concerns would be limited to the potential that a new protein could cause an allergic reaction in some people or could be a toxin.

PHARMACEUTICAL CROPS

FDA has the authority and responsibility for regulating pharmaceuticals, whether they are manufactured in a traditional manufacturing plant or manufactured in crops in the field. For crops in the field, however, there are additional issues to be addressed, including issues involving the parts of the plant that do not contain the pharmaceutical and the residual crop left over after a pharmaceutical is extracted.

In September 2002, FDA and USDA published Draft Guidance for Industry on the use of bioengineered plants or plant materials to produce biological products, including medical devices, new animal drugs, and veterinary biologics. This draft guidance outlines the important scientific questions and information that should be addressed to FDA by those who are using bioengineered plants to produce medical or veterinary products. We are currently reviewing public comments on this guidance.

CONCLUSION

After 10 years of experience in this country, there is every reason to conclude that bioengineered foods are as safe as food produced through traditional breeding techniques. Both the U.S. General Accounting Office (GAO) and the National Academy of Sciences (NAS) have issued reports agreeing with this assessment. We are confident that the foods developed using bioengineering that we have evaluated are as safe as their counterparts, and we will continue to follow the development of this technology to ensure that any new safety questions are also resolved prior to marketing. ❑