Commercialization of Genetically Modified Plants: Progress Towards the Marketplace

Robert T. Fraley
Group Vice President and General Manager
The Agricultural Group of Monsanto Company

This is a very exciting time to be talking about the applications of agricultural biotechnology and especially the commercialization of genetically modified plants. Two events in the first months of 1994—the launch of bST and the approval of Flavr Savr™ tomato—certainly provide a wonderful setting to now talk about real products and real issues as this new industry moves forward. However, the key to putting biotechnology in perspective may not be to look at today's events but to look forward into the future in order to understand the importance of this new technology in agriculture—a technology that is urgently needed to meet the challenge of producing food in an environmentally compatible fashion.

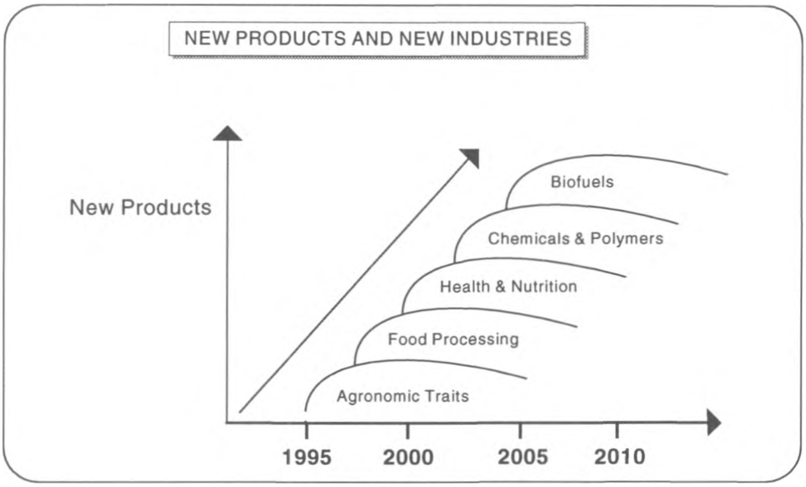
Right now, there are 5.5 billion people on the planet and, almost all experts agree, in another 40 years that number will likely double to 8-10 billion people before stabilization. Forty years is not a long time for any of us. I just had my 40th birthday celebration last year. I have a couple of small boys at home and when they are my age, they will be sharing this planet with 10 billion other people. What we do today and how agriculture prepares for that future will significantly determine the quality of their lives. Producing food—and producing it in a way that addresses both the consumption demand and environmental issues that face agriculture around the world—is a tremendous challenge that we all take very, very seriously.

The magnitude of this challenge can be appreciated when one considers that today the world feeds its 5.5 billion people by cultivating a land area of 5.8 million square miles, about the size of South America. Had we decided in 1950 not to invest in the new agricultural technologies which provided for the productivity increases over the last 40 years, we would be plowing up a land mass the size of North America and South America combined (i.e., about 15 million square miles) in order to meet today's needs for food, feed and fiber. Even greater pressures face us as we look forward. If we do not elect to use new tools that can enhance productivity for the future, 40 years from now we will be plowing up an area the size of all of Eurasia, or over 30 million square miles, to feed those 8-10 billion people. Already the world's most productive and sustainable, farmable land is under cultivation. In addition, the leading cause of species extinction is destruction of the wilderness for farming and forestry. This new technology—biotechnology—-is essential to increase the food supply without having to plow up the entire planet.

NEW TOOLS, NEW OPPORTUNITIES

Considering that the agricultural productivity increases over the last 40 years were driven by significant advances in several areas: plant breeding, farm mechanization, the use of crop chemicals, irrigation systems and modern farm management practices; we certainly need to support these tools and their continued development. In addition, biotechnology is important because it is a new tool—one that we have not yet used—and one that can have a significant impact on the future. For this reason, Monsanto and many other companies and universities around the world have put significant energy and investment into biotechnology. The impact of biotechnology is expected be very, very broad. Plant biotechnology promises to deliver a stream of new products—and new industries (Figure 1). We can already see the first wave of agronomic products as better disease-resistant varieties, new insect control options, better weed control systems, sensitive diagnostic systems are being developed. We can see clearly how biotechnology will lead to new opportunities in food processing by developing foods with different functional compositions as well as fruits and vegetables with better storage properties and flavor. We expect to see significant improvements in health and nutrition through modification of plants to reduce some of the health problems associated with certain fatty acids or removal of particular natural carcinogens. As we look to the not-so-distant future, we can see plants as micro-factories producing specialty biodegradable plastics or producing biofuels which could reduce dependence on our limited petroleum resources. Whole new industries will

FIGURE 1



be starting from the technology that is being developed today in laboratories and fields around the world.

Can biotechnology really have this impact? Over the last 15 years of research, two fundamental breakthroughs have occurred that provide the basis for developing these new products. One, of course, has been the unraveling and understanding of DNA; we now have the ability to isolate genes, study them, modify them and regulate their expression very precisely in different tissues and organs in the plant. The other important advance has been the ability to introduce genes into crops, in very facile ways using *Agrobacterium* vectors or particle gun technology that now allows for improvements using genetic engineering to be made across most of the world's major crops (Table 1).

TABLE 1

CROPS THAT CAN BE MODIFIED BY GENETIC ENGINEERING (1994)

Tomato	Soybean	Petunia	Potato
Cotton	*Arabidopsis*	Lettuce	Sunflower
Eggplant	Peas	Oil Seed Rape	Asparagus
Carrot	Flax	Yam	Cauliflower
Canola	Sweet Potato	Cabbage	Brown Sarson
Orchard Grass	Celery	Tobacco	*S. integrifolium*
Cucumber	Papaya	*H. albus*	Horseradish
Kiwi	*B. rapa*	Morning Glory	Licorice
V. officinalis	Muskmelon	Foxglove	*B. carinata*
Poppy	*M. truncatula*	Strawberry	Lotus
Sugar beet	Pear	Chrysanthemum	Alfalfa
Apple	Carnation	Rye	Apricot
Snapdragon	Rice	Grape	Orchid
Corn	Poplar	Tulip	Wheat
Walnut	Rose	Sorghum	White Spruce
Cranberry			

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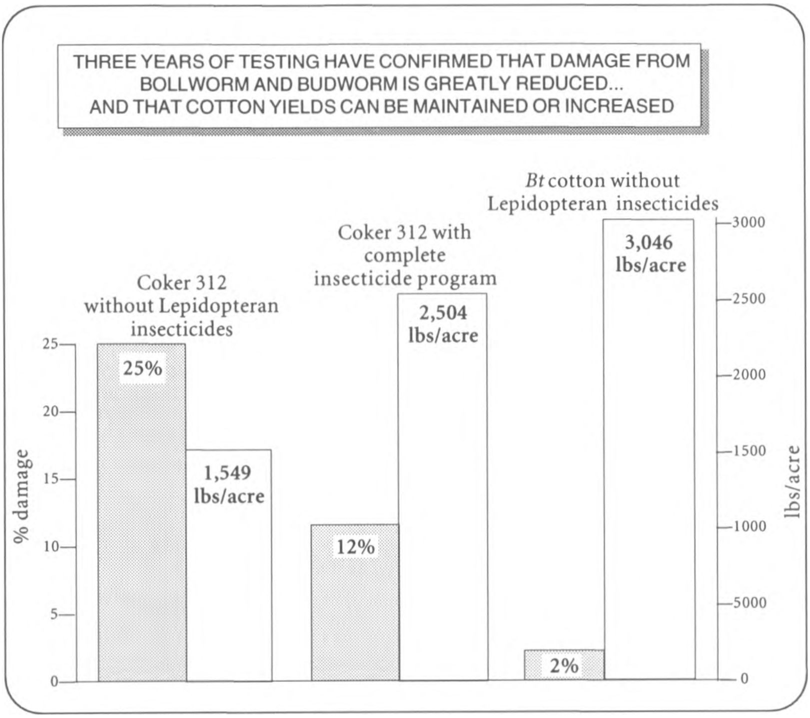
The pace of movement of the technology out of the laboratory into the field has been breathtaking. The first plant genes were isolated in the late 1970s—by the year 2000 we will know almost all of the genes in the model plant, *Arabidopsis*. The first field tests were done in 1987; in 1994, there will be well over 1600 field tests of genetically engineered crops. These include a broad range of species; at least 25 traits are in advanced development, about 10 of which are in the regulatory pipelines of the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA). Dozens of companies and universities are involved in developing these products. Let me briefly describe some of the new products that Monsanto expects to introduce in the next few years and the benefits they will bring to farmers, food processors and consumers.

INSECT PROTECTED CROPS

Insect protected crops will be one of the first products of biotechnology that will have significant impact on crop production. Several insect protected crops, including cotton, potato and corn will be commercialized in the next two to three years. Losses due to insect damage are still very significant with estimates ranging between 30-40 percent of the world's crop production lost due to insect damage. Nature has provided an approach for genetically engineered insect control with *Bacillus thuringiensis (Bt),* a soil bacterium that produces a protein that can kill insects. These proteins have been used in formulated microbial sprays for the last 30-40 years to control pests. Different *Bt* strains have activity against caterpillars and beetles; present microbe-based products control insects but they have shortcomings such as high costs and short half-life in the environment which have kept them from being widely-used products. They account for only one to two percent of all the insecticides that are currently used around the world. One of the ways envisioned to improve these products was to take the gene out of the microorganism and introduce it into the plant so that the plant produces a protein in its leaves that can control insects. This lowers the product's cost as well as providing season-long control of the insect pest. One of the first products that we will be launching will be the cotton plants that are resistant to bollworms, one of the most damaging pests in cotton that farmers must control to produce a crop. We have been field testing this product now for the last four years across the cotton belt in the U.S. and Australia. The data from this testing compares insect control and crop yield with *Bt* cotton to a normal insecticide regime where there is spraying once every seven to ten days. Plants containing the *Bt* protein are completely protected and show less damage than those treated with a very rigorous insecticide spray regime (Figure 2). Less insect damage translates directly to improvements in cotton yield and grower profitability.

The same approach of introducing *Bt* genes into crops has been demonstrated to be applicable for many other important pests. The Colorado Potato Beetle, a big problem in potato production, is controlled when a different *Bt* gene is placed in the potato. Plants protected against the Colorado Potato Beetle are undamaged by insects under conditions in which control plants are completely devoured. Again, we expect this technology will be introduced in the next two to three years. And finally in corn, Bf genes have now proven to be useful in field tests in controlling the European Corn Borer which is a pest that burrows inside the cornstalk. Under conditions of heavy pest infestation the crop will normally have problems standing erect that result both in yield loss as well as subsequent fungal and crop quality problems. Introducing the *Bt* gene into corn provides a new way for controlling these pests. These are important technologies that provide either new pest control systems, FIGURE *2*



substitutes for current practices or new tools that can be used to help manage insect resistance to other products. In our research laboratories, other genes are being developed that control several other important insect pests.

There is another important aspect of this technology that may be more significant to farmers outside the U.S. where many times insect control procedures are less well developed. In these areas, rather than deriving benefits from product substitution, very significant production and storage increase opportunities can be achieved in a variety of fruit, vegetable and row crops through better insect control. We are developing those applications in conjunction with a partner, Delta Pine Land Company, for cotton and with other companies for various crops.

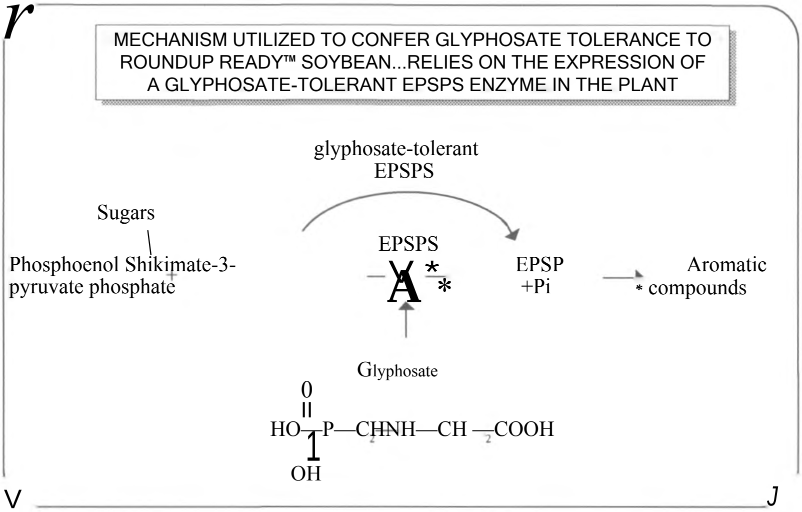
Regulatory packages for the insect-protected cotton and potato have been prepared and submitted to the EPA. Thousands of analyses have been performed to very carefully study the composition of cotton seeds and potato tubers, and no differences in composition of the starches, fats, proteins and oils in these crops have been observed. We have done feeding trials, both with laboratory models as well as with production animals, to show that the feeding and weight gain from cotton meal or potatoes is comparable to the nonengineered crop. We have looked at whether there could be changes in any of the natural toxicants, either solanine in potato or gossypol in cotton. Again, no changes. We have looked at the processing characteristics, the quality of fiber, and the chipping and frying performance of potatoes; again, no difference. The bottom line of literally thousands of pages of documentation and laboratory research conducted by our scientists and academic partners confirms that these plants are completely unchanged except for the properties that we have introduced. Based on this we have concluded that the genetically engineered crops and harvest products are comparable to crops already in production.

ROUNDUP READY™ CROPS

Probably one of the most controversial applications of agricultural biotechnology has been to improve weed control through genetic engineering of herbicide tolerance. Weeds are big problems for farmers. They not only compete with crops for sunlight and moisture but they spread diseases, act as harbors for natural pests and contaminate crop quality. Next to insects, weeds are the biggest pests in agriculture. Monsanto and other companies continue to develop improved herbicides and explore other alternatives for weed control. One of the very attractive opportunities that exists through biotechnology is to take existing products that have good efficacy and established safety and extend their use into new areas by engineering selectivity in the crops. That is the case for our product, Roundup®, a herbicide that is very effective against almost all weeds. By engineering crops to be tolerant to Roundup® herbicide, we have developed new options farmers can use to control damaging weeds. We have been able to achieve this breakthrough with an approach that replaces in the plant the EPSP-synthase target enzyme with naturally-occurring resistant versions of this enzyme that are not inhibited by Roundup® herbicide (Figure 3). This method has produced striking levels of tolerance in crops such as soybeans, canola, cotton and corn.

One of the important questions that people ask is, “Why is this an important technology and what are the benefits to growers and society at large?” In order to answer that question, we must consider one of the other great advances that is going on in agriculture in this country—the adoption of conservation tillage or “no-till” agriculture. Although conservation tillage was originally driven by regulatory compliance, farmers now see economic advantage to applying this practice to soybeans, cotton and corn. When I was growing up on a farm in the Midwest, I remember the scene quite well: deeply plowed, black fields which became very prone to water and wind erosion. Now that is all being very rapidly replaced with direct seeding of the new crop into the previous crop stubble that is being given minimum tillage. The covering mat of crop residue prevents the wind and water erosion that is a big problem for agriculture in many, many areas. So, how can Roundup Ready™ crops help? One of the problems with no-till technology is that weeds can become increasingly bigger problems. New crops with a tolerance to Roundup® herbicide

FIGURE 3



allows for more effective in-crop weed control to mitigate this concern and allow farmers to take full advantage of the many environmental and economic benefits that reduced tillage practices offer.

BETTER TASTING FOODS

The last two products I will describe have direct benefits to consumers. It seems that wherever I have talked over the last several years about biotechnology, there is always a person in the audience who asks, "Well, what are you going to do about my tomatoes, and the taste?" Tomato production in the U.S. is a very organized logistical system that starts when mature green tomatoes are harvested, processed, shipped, transported to the major cities and finally end up in the grocery stores as the red tomato you expect to see. The problem is that when tomatoes are picked green (to have enough shelf-life) they may have not developed their full set of acids and sugars that gives us the flavor of a vine-ripened tomato. So they do not taste as good as they look.

A number of companies, including Calgene, Inc., ZENECA Plant Science, DNAP Corporation and The Agricultural Group at Monsanto Company have developed ways of improving the flavor of the tomato by changing the tomato to better fit into this logistical transport system. This whole process takes about ten days to go from green to red. We have figured out ways of slowing that process down so that it now takes about two weeks. This is important because now tomatoes can be picked when they are at the pink stage where they have developed some color, but more importantly where they have developed all their flavor and can still have sufficient time to be transported to markets across the country. The improved flavor comes from being able to slow down the ripening process so the tomato can be picked at a later stage of ripening.

Biochemically, this process is well understood. The whole process of ripening, going from a green to a red tomato, is triggered by a substance in the plant called ethylene that is produced from an amino acid. We have been able to slow down the production of ethylene by shunting the pathway at a precursor step with an enzyme called ACC deaminase. Pending regulatory approval, we will be in the market in about a year and a half in partnership with a tomato company in Florida called NTGargiulo. Calgene is now in the market with their Flavr Savr™ product. We expect a couple of others. It is a big market; it is a big opportunity; and it is going to have a real benefit to consumers.

The last concept I will talk about is better tasting french fries and potato chips. The science in this case deals with the part of biochemistry—if you took the course, you probably slept through it—that is carbon metabolism and photosynthesis and how plants fix carbon and transport it to their roots and shoots and potato tubers. Let me summarize a lot of work and a really complicated pathway by saying that scientists have now figured out the key steps that actually limit the ability of plants to produce sugar and store it in the form of starch in the potato tuber. By increasing the flow through particular rate limiting steps, we have been able to produce dramatic increases in the starch content in a variety of crops. For example, potatoes normally contain about 19 percent dry weight after they have been genetically improved with the gene to increase the starch content, the starch content can go to 22-24 percent. That is a dramatic increase in tuber starch content; the improvement that has been made historically through plant breeding for comparison has been a little more than a tenth of a percent a year!

There are several benefits of having potatoes with the higher level of starch. To the food processor, having a higher starch potato produces more french fries or potato chips per truckload of potato. So there is clearly a cost savings advantage to the processor. To the consumer, there are other important advantages. Having the higher starch in the potato comes at a consequence of having less sugar in the potato. So during storage when sugars normally are produced in the potato that give rise to the brown-colored french fries or potato chips, the potatoes produced from high-starch potatoes will have the lighter color that most consumers in this country prefer. But the other important advantage of having a higher starch potato is less oily, uniformly cooked french fries or potato chips. The frying process for potatoes essentially displaces water for oil. Having higher starch gives you a faster cooking time because there is better heat transfer, and since there is more starch and less water, there is less oil needed to displace it. So the chips and fries made from genetically improved potatoes consume about 20-25 percent less oil in cooking than do normal potatoes.

CONCLUDING REMARKS

I would like to close with brief discussion of some of the issues which remain ahead of us. The overall progress on regulatory approvals for genetically engineered crops has been very positive. In the U.S., the three lead agencies—EPA, FDA, USDA—have worked together to coordinate oversight responsibilities and develop guidelines; the approval granted to Calgene for their Flavr Savr™ tomato represents a watershed event. Perhaps even more stunning has been the progress made internationally. In Europe, the United Kingdom and France have both moved forward with approvals. In Japan, regulations should be in place by the end of 1994.

Public acceptance, both in the U.S. and internationally, remains an issue—largely manifested through pressure points such as new legislative initiatives, food labeling and international trade. Labeling has been a controversial point with biotechnology products. The arguments on both sides are emotional and persuasive; the FDA has done a credible job of balancing these issues and addressing them in their new food labeling laws which support labeling when: 1. there are changes in identity when traditional standards no longer apply (e.g., broccoflower) and 2. reasons of health or safety (e.g., addition of a known allergenic protein to a new plant variety).

"Voluntary" labeling must not mislead the consumer to suggest that a safety issue or significant difference exists between the traditional and newly developed products. Labeling for process (i.e., genetically engineered) is inconsistent with the above criteria.

Commodity agricultural crops, unlike pharmaceutical products, know no boundaries. Thus even as we produce the first genetically engineered corn or soybean crops in the United States, we must make sure there is international harmonization of regulations—before these grains are shipped to international destinations. Otherwise "non-tariff barriers" could become issues in the future as we have seen happen previously for other agricultural products.