Issues Related to the Development and Use of Engineered Herbicide-Tolerant Crops in California

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Introduction

The 21st century has been dubbed the "Biotech Century" by supporters and detractors alike. In the long term in agriculture, genetic engineering will play an increasingly important role, providing alternatives to the farmer, manufacturer, and consumer. At present, there are issues with genetically modified organisms, or GMOs, related to consumer and environmental safety and labeling. Although this might result in a temporary slowing of the progress in the development of modified crop species, this is not likely to stop the use of the technology in the long-term. The products of the new genetic technologies, if used wisely, will provide a variety of improvements in crop species in the long term.

Methods have been devised to identify the genes involved in specific traits in addition to the ability to introduce one or a few of these genes into many different crop species. These gene introductions can result in very specific changes in a particular trait without affecting the overall performance or characteristics of the plant. Some examples of these altered traits include improved disease and pest resistance, changes in post-harvest or processing traits, alterations of nutritional or antinutritional qualities, and improvements in agronomic traits, like enhanced nitrogen utilization and herbicide tolerance.

Indeed, products produced from such biotechnological approaches are no longer just a promise; much is reality. Currently there are crops in the field and products in the marketplace that have been genetically engineered and are being eaten by consumers. In the summer of 1999, the percentage of actual production acreage that was genetically enhanced in the U.S. was 50% of cotton, 55% of soybean, 40% of maize and 3% of potato (1).

The products that are in commercial production today represent only the first, rather crude attempts to use engineering to improve crop plants. More, much more is on the way. According to U.S. Department of Agriculture records, over 4,500 genetically-enhanced plant varieties have been field-tested in this country, more than 1,000 in the last year alone. About 50 engineered varieties have already been approved for unlimited release (deregulated), including 13 varieties of corn, eleven of tomatoes, four of soybeans, two of squash, and even one type of radicchio. Hundreds more are in the pipeline, among them plants that will produce industrial compounds, such as industrial oils, substitutes for gasoline and biodegradable plastics. There is also work in progress to use plants such as corn, potato, and banana as mini-factories for the production of vaccines and other medicinals; foods that can help prevent a variety of diseases, such as Type II juvenile diabetes.

To date, herbicide-tolerant crops (HTCs) created through biotechnology are the most frequent application of genetic engineering to crop plants. This is because herbicide resistance is
a simple, easily engineered trait that to date involves only a single gene. The biochemistry of tolerance to certain herbicides is well understood, and it has allowed companies to link the sale of GM HTCs to the sale of their proprietary herbicides. At present, most engineered herbicide-tolerant varieties involve two herbicides: glyphosate marketed by Monsanto as Roundup; and phosphinothricin, or glufosinate, marketed by AgrEvo under various brand names such as Basta, Finale, and Liberty. Examples of California crops that are being engineered for glyphosate tolerance are corn, cotton, lettuce, rice, soybean, sugarbeet, tomato and wheat. Crops engineered for phosphinothricin tolerance include canola, chicory, alfalfa, corn, melon, rice, sugarbeet, tomato, cotton, and soybean.

Another combination of herbicide and HTC is the Imi-rice variety coupled with imidazolinone-type herbicides being developed by Dupont. The development of this HTC resulted not from genetic engineering *per se* but from the chemical induction of a mutation that results in herbicide tolerance. Currently, "Roundup-Ready" cotton is the only HTC to have been commercially grown in California. During the 1999 growing season, 5% of California's cotton was the Round-up Ready variety.

HTCs can play an important role in agriculture if they are properly managed since they provide some distinct advantages for the farmer in combating weed problems and providing the opportunity for lower or no-till agriculture. As the utilization of this technology continues, herbicide-tolerant field and vegetable crops may become commonplace in California production systems. These products are not likely to be "magic bullets" that will provide quick solutions to the problems of weed control. However, they will provide useful, complementary tools in the grower's arsenal by offering weed management alternatives, which can help address weed control problems. Along with this benefit, however, come issues relating to proper weed management and concerns relating to the economic, environmental, and consumer acceptance issues involved with their use.

**Technical background**

Both glyphosate and glufosinate are potent, broad-spectrum herbicides that are highly effective against the majority of grasses and broad-leaf weeds. The particular biochemical pathways affected by these herbicides occur only in plants and microorganisms, which explains the relative lack of toxicity of these chemicals to other living organisms.

*Glyphosate* - The herbicide glyphosate (N-phosphonomethyl-glycine) is chemically a simple tertiary amine. Its primary cellular target is an enzyme, EPSP synthase (5-enolpyruvyl-shikimate-3-phosphate synthase), involved in the synthesis of aromatic amino acids and other essential aromatic compounds in the plant. Three main genetic engineering strategies have been implemented to confer glyphosate tolerance in transgenic plants: 1) using a bacterial gene that specifies a mutant form of the target enzyme, which is no longer susceptible to glyphosate; 2) producing larger quantities of the native target enzyme or using a more active, mutant enzyme in an attempt to compensate for the enzymatic activity that is disabled by the herbicide; or 3) introducing a bacterial gene responsible for glyphosate degradation, termed glyphosate oxidoreductase or GOX, which produces an enzyme that catalyzes glyphosate degradation.
Glufosinate – Phosphinothricin, the active component of glufosinate, is structurally similar to the amino acid glutamine and, as such, selectively inhibits the biosynthetic enzyme that produces glutamine, i.e. glutamine synthetase. This inhibition leads to the intracellular accumulation of ammonia, the cessation of photosynthesis and the disruption of the chloroplast. Tolerance has been engineered in plants by using an enzyme, PAT (phosphinothricin acetyl transferase) that inactivates the herbicide by acetylation. The gene encoding this enzyme is derived from a soil bacterium, which naturally makes a phosphinothricin-containing compound.

Generation of herbicide-resistant weeds

A major concern with HTCs is that their use will promote the overuse of their associated herbicide. Overuse of a particular herbicide often leads to the generation of herbicide-resistant weeds. Such weeds would render the herbicide obsolete, thus removing it from the farmer’s weed control arsenal. There are certain characteristics of herbicides or their use that make them more likely to promote the development of herbicide-resistant weeds. These include single target sites for the herbicide, long soil residuals, season-long use to control germinating weeds and/or frequent and long-term application of a particular herbicide without alternating or combining it with other herbicides having different modes of action. Mono-herbicide application (continual application of a single herbicide or herbicides with similar modes of action) is known to increase the rate at which herbicide-resistant weeds arise. It is likely that continual use of either glyphosate or glufosinate without rotation will lead to the development of herbicide resistant weeds. Therefore, the employment of HTCs needs to be carefully managed if their long-term use is to be assured.

Glyphosate is considered low-risk for leading to the evolution of herbicide-resistant weeds. Its mode of action, chemical structure, limited metabolism in plants, use-pattern, and lack of residual activity are often cited as reasons why this herbicide is unlikely to select for resistance. However, this is low-risk, not no-risk, and glyphosate resistance in rigid ryegrass (Lolium rigidum) has been discovered in both Australia and the United States. In Australia, glyphosate-resistant rigid ryegrass was identified near an orchard in 1996 (4). This orchard had intensive selection pressure, with two or three applications of Roundup per year for 15 years to control weeds within rows of trees. Further studies showed that the resistant weed population was nearly 10-fold more resistant to glyphosate than susceptible biotypes (5). In California, glyphosate-resistant rigid ryegrass was also discovered in 1998 in a field that had received repeated applications of glyphosate (6). Another more recent study reported on research attempting to determine the mechanism of resistance in ryegrass (7). There were no significant differences in uptake, translocation or metabolism between resistant and susceptible weeds suggesting that changes in the glyphosate-binding site on the EPSP synthase enzyme or overexpression of the enzyme might be the source of resistance in this biotype.

In addition to the glyphosate-resistant ryegrass examples, Monsanto scientists have described a glyphosate-resistant goosegrass (Eleusine indica) (8). The problem weed appeared in 1997 in oil palm plantations of Malaysia where as many as eight annual applications of glyphosate have been made for the past 10 years. This resistance is caused by a single amino acid substitution in the glyphosate-binding site of the EPSP synthase enzyme, which causes the goosegrass to be up to five times more tolerant of glyphosate than susceptible plants. The
glyphosate resistant goosegrass has appeared on four oil palm plantations and already infests approximately 12,500 acres. Goosegrass is one of the major annual grass weeds in the tropical and subtropical regions of the world, and is considered among the most troublesome weeds in the world. The appearance of glyphosate resistance in major world weeds, like rigid ryegrass and goosegrass, emphasizes the importance of good, integrated weed management and careful use of selective herbicides to preserve the efficacy of glyphosate and other important herbicides.

Another way that encourages the emergence of herbicide-tolerant weeds is through the spread of herbicide tolerance genes to wild species, to sexually compatible weeds or to non-engineered plants, such as those being cultivated under organic standards. Of all traits being introduced by genetic engineering, herbicide tolerance is the one most likely to result in observable gene movement to other plants since observation of the presence of the tolerance gene is easily seen following herbicide application. Genes for tolerance could certainly be transferred to related weed species from the engineered crops; however, the situation can be managed to prevent or minimize the problem. Some of the weeds that are potential recipients of herbicide tolerance genes from cultivated varieties are among weeds that are most difficult to manage; examples include weed species that cross with the major cereal crops, such as Johnson grass and red rice. In the United States, most crops do not have weedy relatives with which they can outcross; exceptions are canola, carrots, certain cucurbits, lettuce, oats, radish, rice and sugarbeet.

Farmers must be very cautious about using herbicide tolerant varieties in areas with sexually compatible weed species. Weeds in the general vicinity of the herbicide-tolerant crop, with which the modified plants might outcross, are likely to be kept under control by herbicide application and therefore not reach a reproductive state at all or certainly not at the time when pollen would be shed from the engineered plant, thereby minimizing the likelihood of sexual exchange between the two species. Therefore, unless pollen travels over long distances and pollinates weeds located at a considerable distance from the cultivated plants, where herbicide application does not occur, this problem can be minimized or eliminated by careful application of herbicide. Another means of managing the transfer and perpetuation of the herbicide tolerance gene in weed populations is to alternate the type of herbicide used or to use another herbicide to control the weed population during the season. A third solution would involve the use of so-called gene protection systems, the best known of which has been called the terminator technology. The latter system results in plants that cannot reproduce themselves because embryo development in the transgenic plant is halted. By using plants engineered with such a system in areas having sexually compatible weed or wild species, it would be impossible to perpetuate the herbicide tolerance gene in other plants.

Weed-shifts are another problem that may make harder-to-control perennial weed species a problem. Weed-shift refers to a change in species composition in an ecosystem due to the systematic elimination of those species that are well controlled by the herbicide and proliferation of those species that are naturally tolerant of the herbicide. This can result from the repeated use of herbicides with the same modes of action and occurs because the application of a single herbicide creates a favorable environment for weeds not completely destroyed by the herbicide.

Development and utilization of germplasm tolerant to a single herbicide, without comparable development of cultivars tolerant to other herbicides with dissimilar modes of action,
would likely exacerbate both the herbicide resistant weed and weed-shift problems. One way industry can promote the use of multiple herbicides on the same acreage is to work collectively to develop similar cultivars that have tolerance to herbicides with different modes of action and spectra of control. Farmers could then utilize crop rotation with the different engineered crops. If farmers can purchase their preferred cultivars with tolerance to herbicides with different modes of action, then herbicide rotation is more likely to occur. Alternatively, different tolerances to herbicides could be engineered into the same cultivar, and the herbicides then used in rotation. The difficulty with this approach is that at present the different chemistries belong to different companies and it is not likely that they would agree to introduce their genes together in the same plant. Either approach is likely to reduce problems due to weed shift, the emergence of herbicide resistant weeds and herbicide-tolerant volunteers arising from the previous crops sharing the same herbicide tolerance. The successful long-term use of HTCs must involve herbicide rotation in order to minimize many of the problems listed above. Herbicide alternatives not linked to the engineered crop will also likely still be available and used in order to maximize the utility of HTCs.

If farmers are to benefit from these technologies and companies to recoup their development costs, herbicide-tolerant crops must be used as a part of an integrated weed management program. For example, the use of a particular herbicide and its associated HTC must not be continuous. Properly informed farmers and well-implemented and monitored regulatory policies will help curtail mono-herbicide application and mono-herbicide tolerant crop use. While a good choice in theory, herbicide tolerant crops of certain species might not be available that have tolerances to herbicides with different modes of action. Therefore, replanting of a particular HTC over several seasons might be likely occur if the farmer realizes savings on inputs. Additionally, in the near-term it is likely that most crops used in rotations, like soybean and corn, for example, will be engineered for tolerance to the same herbicides. This also increases the likelihood of continuous mono-application of a herbicide with the same mode of action.

Anticipation of problems, such as those listed above, has led to the organization of inter-company groups, such as the Herbicide Resistance Action Committee (9), which exchanges information on the development and spread of herbicide-resistant weeds and develops guidelines for managing resistant weeds. Inter-company cooperation in the development of HTCs, as outlined above, is imperative to avoid weed-shift problems and the development of herbicide-resistant weeds. In addition, companies must work closely with university and extension personnel during the development and deployment of HTCs in order to determine how they and their associated herbicides perform in particular areas and how to avoid potential environmental problems.

**Economic**

Proponents of HTCs assert these crops should prove profitable over nonGM crops because of reductions in herbicide costs and increased crop yields. However, evidence to date is sketchy and hard to come by that these claims are true. An Iowa State University report, for example, states that in 1998 Iowa soybean farmers using Roundup-Ready (RR) seed saved roughly 30% on their herbicide costs, but that yield drag caused a loss of 2 bushels per acre (10).
This meant that total cost per acre for GM and nonGM soybean was about the same. Yield drag in these varieties is believed to be due to the fact that the particular soybean varieties into which the RR gene is introduced are not varieties that are expected to give optimal yields at all locations.

Charles Benbrook, an independent biotechnology consultant, recently published a review on RR soybean drag based on the results of over 8200 university-based soybean varietal trials performed in eight Midwestern states (11). His report concluded that in 1998 RR soybean varieties yielded 5 to 10 percent less on average compared to all varieties tested. Benbrook suggested that so far the RR seed technology is at best an economic wash. He stated that despite their cost RR soybeans are popular with farmers because they are tired of dealing with the complexity, cost and periodic failures of other soybean weed management systems.

Current RR soybeans yield less probably because the engineered traits were not introgressed into crop varieties that perform best in different growing regions. In the future companies developing HTCs should work with breeders, public and private sector, to introgress herbicide tolerance traits into cultivars adapted to perform optimally for specific growing regions. And the breeders should realize some economic benefits for participating in this aspect of the development of the optimized-engineered variety.

Environmental

Numerous herbicides are widely used at present as part of weed control programs. Of these herbicides, glyphosate and glufosinate are considered, in general, low use-rate, low-toxicity, rapid-turnover herbicides. Therefore, the increased use of these herbicides should result in lower environmental impact than occurs at present with the higher impact herbicides. Glyphosate and glufosinate have minimal mammalian toxicity and show little, if any, leaching into groundwater. This latter benefit should prevent additional groundwater pollution in California caused by the herbicides, atrazine, simazine and diuron. Rotation of cropping systems with engineered and non-engineered varieties of the same crop species could also encourage the rotation of herbicide usage, thereby reducing environmental buildup of the utilized herbicides.

Will the existence of engineered herbicide-resistant crops increase the use of certain herbicides and will their existence perpetuate farming’s dependence on herbicides? The adoption of HTCs will certainly result in an increase in sales of the herbicides to which tolerance is being engineered. An increase in sales does not imply, however, that farmers are applying more herbicide per acre. In fact, a recent USDA report indicates that in 1997 herbicide-tolerant technology significantly reduced herbicide treatments for soybeans and, to a lesser extent, for cotton in most regions of the U.S. (12).

Consumer Acceptance of Products of Biotechnology

Genetic engineering or biotechnology is a new technology that is being used to modify foods. When new technologies are introduced into food production, there are often consumer concerns. For example, there were furors over pasteurization, microwave ovens and food irradiation. Biotechnology will not be an exception. Over the last decade, numerous
scientifically conducted polls were conducted to gauge consumer acceptance of foods produced with biotechnology. Up until recently these surveys in the U.S. have found that between 2/3 and 3/4 of consumers are supportive of biotechnology.

The trend toward acceptance was seen in a survey conducted in the U.S. by the International Food Information Council (IFIC) in February of this year. In that survey, the majority of U.S. consumers were willing to "purchase a food modified by biotechnology to taste better or fresher" (62%) or a food "modified by biotechnology to be protected from insect damage and requiring fewer pesticides" (77%).

Another recently released poll was conducted by Gallup on September 23-26, 1999. Respondents in the Gallup poll were asked to rate the likelihood that biotechnology poses a serious health hazard to consumers: 53% thought it did not present a serious hazard, 20% were unsure, and 27% thought it posed a serious hazard. Despite this expressed fear, respondents expressed confidence in the U.S. Food and Drug Administration, the regulatory arm that monitors genetically engineered food products. Seventy-six percent of Americans had a great deal or fair amount of confidence in the federal government to ensure the safety of food.

Interest in labeling, as evidenced in the Gallup poll, has risen dramatically over previously conducted polls with over 2/3 of respondents in favor of labeling. This is despite the possibility of an increase in price. The increased interest in labeling and the rising consumer concern in the U.S. is likely due to the fact that anti-GMO sentiment was high in Europe and consumer concern was being fed by scare scenarios of the effects of GMOs. Newspaper accounts of this turmoil were seen in the U.S. almost daily.

The intense feelings of European consumers against GMOs came about because of some fundamental differences in issues and occurrences between Europe and the U.S. Perhaps the most significant events influencing consumers feelings about GMOs were the food scares that occurred recently, including mad cow disease and dioxin contamination. The pronouncements and decisions made by governmental officials during these controversies were perceived by many to be based on political expediency rather than on public safety concerns. This undermined consumers’ confidence in the government to assure food safety with biotech foods and led to more open minds for activists’ claims.

Once tensions and accusations reached a certain peak in Europe, activists decided to focus their anti-biotechnology efforts on Canada and the U.S. A very significant early event in their campaign in the U.S. was getting baby-food giant, Gerber, to agree not to use GMOs in their baby food. After this pronouncement several other large companies followed suit. Perhaps the most significant was Archer Daniels Midland (ADM), one of the country's largest grain handlers. ADM decided in late summer of this year to demand that their suppliers segregate GM from non-GM grain. This they said had to do with “a change…in consumer demand”. International trade had become a question: what products would and would not be accepted in Europe? Would they have to be guaranteed to be GM-free? Soon food processors, like ADM, wanted crops segregated and paid premiums to farmers for GM-free grain. But the momentum is not all in that direction. More recently another large processor, Cargill, has promised to take all grain, segregated or not, and find markets for it. Kellogg also has stood firm in its intent to use GM ingredients in its cereals.
How will the whole labeling and public acceptance scenario play out? It is difficult to make predictions for the short-term (2-5 years), but it is likely that in ten years the technology will pervade agriculture. Why? The goals that can be achieved uniquely with this technology will build on the information that will be gained through the study of the genome. This new information will provide new avenues for crop improvement that cannot be achieved in any other way. These benefits will be realized by the consumer and in improvement in the environment.

The first products of the technology are crude; the Roundup Ready soybean is not the best that can be done in terms of an HTC. Many of these products will not achieve the potential necessary for user or consumer acceptance. But the strategies will be improved and refined, just as the computer has moved from a machine that took up city blocks to one that fits on your wrist. Some products of the technology will find favor with users and consumers; some will not. Some will be a commercial success; some will not. But in the long-term, biotechnology is likely to find applications and result in products that will be important tools in the farmer’s toolbox and that will be accepted and likely even sought after by consumers.

Summary

Over the past decade progress in the generation of engineered herbicide-tolerant crops has been rapid with the major acreage crops in the United States, namely corn, cotton, and soybean. These herbicide-tolerant varieties can play an important role in production agriculture if they are properly managed since they provide some distinct advantages for the farmer in combating weed problems and providing the opportunity for lower or no-till agriculture. While these approaches are important for high-acreage crops, their importance for minor acreage crops, including many of California's fruit, vegetable and nut crops, is likely to be limited in the near term. The engineering of minor-acreage crops is not likely to progress at the same rate as that for the major crops because the economic gains do not justify the expenditure by agrochemical companies in developing them. Minor-acreage crops are likely to benefit indirectly from efforts in major acreage crops since progress in these crops will also likely yield new tools or herbicides for use with minor-acreage crops. As engineered herbicide-tolerant crops become available to growers, questions relating to their use will be raised and answered. Currently consumer fears and international trade issues will be one important factor affecting the desirability and utility of HTCs. With time these issues will be resolved at which point the focus will be more on the development of appropriate management systems to control weed shift, weed resistance and outcrossing; these approaches will change as growers integrate this technology into their production systems. Despite the definitiveness of the change, the precise manner in which the availability of these crops will lead to change and exactly what those changes will be are difficult to predict. Only experience with these crops in the fields will give precise answers to the economic and environmental questions raised by their use.
References


(2) Source: USDA at http://www.aphis.usda.gov/

(3) R. Vargas, personal communication.


(9) www.plantprotection.org/HRAC

(10) AgBiotech Reporter, November 1999
