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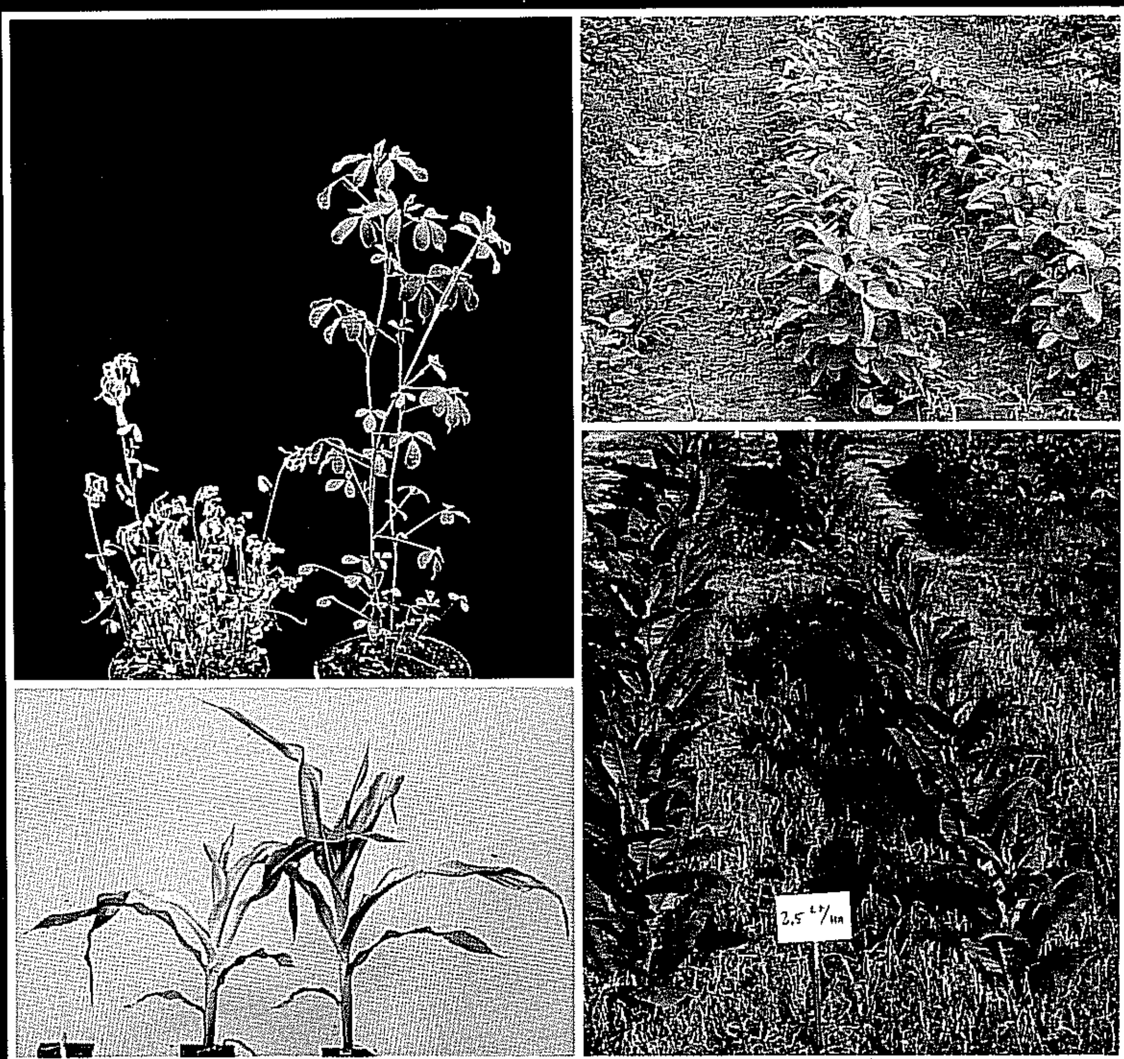
Herbicide-Resistant Crops



Comments from CAST 1991-1
May 1991

Council for Agricultural Science and Technology

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Comments from CAST
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Cover Photographs

Upper left. Glufosinate-resistant alfalfa. Untransformed (left) and transformed RA_3 (right) alfalfa one week after treatment with 2 kg glufosinate per hectare. Photograph courtesy of Hoechst AG.

Upper right. Glyphosate-resistant soybeans (two center rows) sprayed with glyphosate. The nongenetically engineered plants in the row on the extreme left have been treated with the same rate of glyphosate. Photograph courtesy of Monsanto Agricultural Company.

Lower left. The reponse of a nonselected line (left) and two corn lines selected for tolerance to sethoxydim (middle and right) to 0.44 kg sethoxydim/ha. These plants were regenerated from sethoxydim-tolerant or nonselected callus cultures. The photographs were taken approximately 10 days after application of sethoxydim. Photograph courtesy of Department of Agronomy and Plant Genetics, University of Minnesota.

Lower right. A tobacco field trial with glufosinate-resistant transformed tobacco in France two weeks after treatment with 0.5 kg glufosinate/ha. In addition to good weed control, a nice mulch is formed by the killed weeds. The mulch protects the soil from erosion, suppresses germination and growth of new weeds, and serves as a nitrogen supply to the crop. Photograph courtesy of Hoechst AG.

Foreword

In May 1990, the CAST National Concerns and Executive Committees recommended that CAST prepare a Comments from CAST report addressing herbicide-tolerant crops. Dr. Stephen O. Duke, Director of the Southern Weed Science Laboratory, Stoneville, Mississippi, was selected to serve as chair. A highly qualified group of scientists was chosen to write this report.

All authors were responsible for writing the first draft, revising all subsequent drafts, and reviewing the proofs. The CAST Executive and Editorial Review Committees reviewed the final draft. The CAST staff provided only editorial and structural suggestions. The authors are responsible for all scientific content in the report.

On behalf of CAST, we thank the authors, who gave of their time and expertise to prepare this report as a contribution of the scientific community to public understanding. Also, we thank the employers of the authors, who made the time of the authors available at no cost to CAST. The members of CAST deserve special recognition because the unrestricted contributions they have made in support of the work of CAST have financed the preparation and publication of this report.

This report is being distributed to members of Congress, the U.S. Department of Agriculture, the Environmental Protection Agency, the Food and Drug Administration, the Agency for International Development, Office of Technology Assessment, Office of Management and Budget, media personnel, and to institutional members of CAST. Individual members of CAST may receive a copy upon request. The report may be republished or reproduced in its entirety without permission. If copied in any manner, credit to the authors and CAST would be appreciated.

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Summary

All crops are naturally tolerant to some herbicides. Virtually all agronomic crops are treated annually with at least one herbicide to manage associated weeds. Modern biotechnology has provided the capability to make crops resistant to herbicides to which they are normally sensitive. Thus, these methods will offer the farmer more choices in choosing a herbicide for a particular crop. Used properly, this technology can be directed toward production of crops resistant to herbicides that are toxicologically and environmentally less suspect than those herbicides now used with some crops. Also, there will be opportunity to reduce the number and quantity of herbicides applied, and to enhance the use of no-till or minimum tillage systems.

The genes coding for herbicide resistance can be from the crop gene pool or from organisms such as bacteria that are far removed from the crop. Although the technology for introducing foreign genes into crops has become sophisticated, the resulting crop plant cannot always be guaranteed to have all of the agriculturally desirable traits of the nonmanipulated crop. In some cases, this problem has slowed and may continue to slow the development of herbicide-resistant crops using biotechnology.

Another factor that may prevent the full utilization of herbicide-resistance technology is economics. Even if herbicide-resistant crops are technologically successful, the cost of the bioengineered crop seed plus the herbicide to which it has been made resistant must be less or at least equal to existing options that provide the same level of weed management. This technology must compete with continued introduction of new herbicides for use with major agronomic crops. The direct and indirect costs of registration and labeling of herbicides for minor crops will preclude development and introduction of herbicide-resistant minor crops in some cases. Furthermore, the crop seed industry has economic concerns about whether herbicide-resistant crops will benefit them. Thus, simply because this technology may be feasible does not mean that it will play a major role in weed management.

There are concerns about how adoption of herbicide-resistant crops might affect food quality, the environment, genetics of natural populations of noncrop plant species, and rural sociology. No generalizations can be made to address these concerns. Each one will be affected differently depending on the source and type of gene conferring resistance, the crop, the herbicide or herbicides to which resistance is conferred, and the existing methods of weed management for the crop. Existing federal and state regulatory agencies have the capability and mandate to examine and regulate the introduction and use of herbicide-resistant crops on a case-by-case basis. After appropriate environmental and toxicological safeguards have been met, the impact of this technology on agriculture should ultimately be decided by its utility and economic factors.

Several recommendations are made. First, **unnecessarily high levels of resistance that would permit the use of herbicides at much higher than the recommended rates for good weed management should be avoided.** Moderate levels of resistance will prevent the misuse of herbicides on herbicide-resistant crops. The cost of herbicides will normally prevent such misuse. However, in the cases of some home gardeners who may have no economic restrictions or where herbicides become very inexpensive due to expiration of patent protection or other factors, a narrow but practical window of crop resistance would be desirable.

Second, **public funding of research on herbicide tolerance or resistance should not be restricted by legislation.** Past publicly-funded research in this area has resulted in some of the most important fundamental research discoveries of the past decade in the areas of plant biochemistry, plant molecular biology, plant physiology, plant cell biology, and plant physiological ecology. The scientific spinoff from this research has been important in advancing our knowledge of plant science and can be expected to ultimately result in improvements in agriculture in areas unrelated to weed management.

We recommend that **crops should not be made resistant to herbicides which, for environmental or toxicological reasons, are not good substitutes for currently used herbicides.** The herbicide to which the crop is made resistant should be an equal or better alternative to the herbicides already used with the crop.

In the areas where crops and associated weeds freely interbreed, **the crop should not be made resistant to herbicides by biotechnology without also introducing genetic barriers to outcrossing.** There is no evidence that weeds have ever developed tolerance to a herbicide by outcrossing with naturally tolerant crops. However, biotechnologists should take measures to prevent this from occurring with herbicide-resistant crops that they have generated.

Introduction of herbicide-resistant crops should be accompanied by recommendations to farmers for management of the selection for and spread of weed resistance to herbicides. With herbicides to which resistance can most readily occur, this should be a requirement to minimize increases in herbicide resistance in weed populations due to the introduction of a herbicide-resistant crop.

Finally, **the International Food Biotechnology Council's recommendations and guidelines for genetically engineered crops should be followed to protect the public from potential harmful secondary effects of the genes that confer resistance.** There is always the unlikely possibility that a new gene in a plant might generate a new toxin, increase levels of already existing toxins, or decrease the nutritional value of a crop.

1 Introduction

Herbicides are used on virtually every acre of agronomic row crops in the United States and also are used extensively in horticultural crops. At present, crops must be naturally tolerant[1] to the selective herbicides with which they come into significant contact, and that are used in their production. Thus, a major limitation in the selection of a herbicide for a particular crop is tolerance to the herbicide. This limitation influences weed management efficacy, farm economics, and the environment. Biotechnology and, to a lesser extent, traditional plant breeding offer methods of enlarging the spectrum of herbicides that can be used with particular crops.

A recent report entitled *Biotechnology's Bitter Harvest: Herbicide-Tolerant Crops and the Threat to Sustainable Agriculture* (Goldburg et al., 1990) has caused considerable controversy over biotechnology research to generate crops that are resistant to herbicides to which they are currently susceptible. This report by the Biotechnology Working Group[2] (BWG) outlines the research being conducted to promote production of herbicide-resistant crops and assesses the potential effects of this new technology. It presents a generally negative assessment of such research in terms of its perceived impact on the environment, rural sociology, and the farm economy. Those in favor of this new technology are accused of making false promises. No clear benefits of genetically engineered or bred herbicide-resistant crops are acknowledged. The BWG report concludes with a case for sustainable agriculture. To those authors, the definition of sustainable agriculture appears to include the assumption that agriculture with pesticides is not sustainable.

Our report addresses herbicide-resistant crops from several standpoints, including an agricultural viewpoint that we think was inaccurately presented in the BWG report. The outline of our report is similar to that of the BWG except for the deletion of the section on alternative agriculture and the addition of sections on economics and regulation. We do not discuss herbicide-resistant trees because we did not have access to sufficient information to make recommendations in this area. We have chosen not to include a discussion of alternative agriculture because it is a separate issue dealt with in a separate, recent CAST report (CAST, 1990). The BWG report appears to be based partly on the assumption that biotechnological creation of herbicide-resistant crops will be very successful from a purely technological standpoint. No consideration of the probable degree of success of this technology, its acceptance by the farmer, and its adoption by the seed and herbicide industries are discussed in the BWG report. These important considerations are addressed in this report.

[1]The terms tolerant and resistant are often used interchangeably. However, most scientists working in this area of research term naturally-occurring lack of response to a herbicide as tolerance. Resistance has been reserved for cases in which repeated use of a herbicide has resulted in decreased response of a population of weeds through selection for more insensitive individuals of that species. Resistance also refers to plants that are made insensitive to a herbicide by biotechnology. This is how these terms will be defined in this document.

[2]The Biotechnology Working Group is composed of environmental activists and representatives of environmental interest and other special interest groups such as the Environmental Defense Fund, Friends of the Earth, and the National Wildlife Federation.

2 Current Efforts in Research and Development of Herbicide-Resistant Crops

Methods of Generating Herbicide-Resistant Crops

There are three physiological mechanisms by which a plant can be tolerant or resistant to a herbicide. All of these mechanisms can be found in plants that have not been genetically manipulated (tolerance). The first mechanism is **reduced sensitivity at the molecular site of action**, due either to a greatly increased number of molecular sites (amplification) or to an altered site of action. For example the aryloxyphenoxypropionate herbicides (e.g., diclofop, haloxyfop) act by inhibiting the enzyme, acetyl-CoA carboxylase (ACCase). However, only the enzyme from certain grass weeds is sensitive, leaving broadleaf weeds tolerant to these herbicides (Lichtenthaler, 1990). The second mechanism is **degradation of the herbicide by metabolic processes**. This is the mechanism by which most crop plants are already tolerant to many herbicides. For example, all non-genetically engineered crops with which sulfonylurea herbicides are used are already tolerant by virtue of metabolism of the particular sulfonylurea herbicide used with that crop (Mazur and Falco, 1989; Sweetser et al., 1982). This mechanism rarely provides a high level of tolerance. The third mechanism is **avoidance of the herbicide through lack of uptake or by sequestration if the herbicide is absorbed**. For example, cotton is tolerant to post-emergence applications of some triazine herbicides because the herbicide is preferentially absorbed into the glands that cover the stems, cotyledons, and leaves of cotton plants (Foy, 1964). Some weeds that have been selected for by many applications of paraquat are apparently resistant to paraquat due to sequestration of the herbicide (Fuerst et al., 1985).

The first two of these mechanisms (site-of-action and metabolism) by which crops and weeds are naturally tolerant to herbicides have been employed by biotechnologists to generate herbicide-resistant crops. Site-of-action alterations in plants have been utilized in some cases. For example, sulfonylurea- and imidazolinone-resistant crops have been produced by selecting for cells with resistant acetolactate synthase (ALS), the molecular site of action of these herbicides (Haughn et al., 1988, Lee et al., 1988). Selection of callus cultures for sethoxydim resistance has resulted in production of sethoxydim-resistant corn with an altered site of action (Parker et al., 1990) (Figure 2.1B). In some cases of glyphosate resistance that have been selected for in cell lines, the molecular site is present in many more copies than in the susceptible version of the species (Goldsbrough et al., 1990; Steinrucken et al., 1986). Thus, the herbicide is less effective because it cannot inhibit all of the molecular sites at doses that are normally applied. Herbicide detoxification mechanisms normally found in plants tend to be biochemically complex and none have been exploited by biotechnologists (Quinn, 1990). However, microbial genes for herbicide degradation have been used successfully to confer herbicide resistance on crops. For example, bromoxynil-resistant crops have been produced by transferring the gene from a soil bacterium that codes for an enzyme that degrades bromoxynil (Stalker and McBride, 1987). Also, a microbial gene that codes for an enzyme that detoxifies glufosinate has been used to make crops resistant to glufosinate (DeBlock et al., 1987) (Cover photograph and Figure 2.1A, C, and D).

Traits that provide resistance or tolerance can be bred into crops by traditional plant breeding; however, this method is limited by the germplasm diversity for the crop and any closely related species with which it may be crossed. Furthermore, plant breeders have not placed great priority on using existing genetic variability to generate herbicide-tolerant crops. Exploitation of the germplasm of the crops or closely related species to confer herbicide resistance can be accelerated by screening at the tissue culture or suspension culture level or by protoplast fusion or embryo rescue methods. Specific examples of these methods are published (Anderson and Georgeson, 1989; Austin and Helgeson, 1987; Chaleff and Ray, 1984). Recombinant DNA methodologies offer the possibility of inserting genes from any organism into the crop. For instance, a microbial gene that codes for an enzyme that degrades the herbicide can be inserted into the crop genome to make the crop resistant to the herbicide. The glufosinate-resistant crop mentioned

Figure 2.1. Examples of herbicide-resistant crops.

A. Wild type Wisconsin 38 (left) and transformed W 38 (right) tobacco treated with 2 kg glufosinate/ha (3 times the normal application rate). The transformant contains a specific enzyme that detoxifies the herbicide rapidly by acetylation. Photograph courtesy of Hoechst AG.

B. The response of the wild type (left) and homozygous sethoxydim-tolerant S2 (right) corn lines to sethoxydim in the field. Photograph courtesy of Department of Agronomy and Plant Genetics, University of Minnesota.

C. Glufosinate-resistant (left) and susceptible (right) sugarbeets 20 days after treatment with glufosinate. Photograph courtesy of Plant Genetic Systems, N.V.

D. A mixture of weeds, volunteer corn, and glufosinate-resistant corn one week after treatment with 2 kg glufosinate/ha. Only the glufosinate-resistant corn is still alive. Photograph courtesy of Hoechst AG.

above is a successful example of this.

In many cases, conferring resistance to a particular herbicide may also confer resistance to other herbicides that affect the same molecular site of action. Although hundreds of commercial herbicides have been marketed, they affect relatively few molecular sites (Duke, 1990). Thus, the potential for cross resistance to herbicides with similar mechanisms is great.

Public Sector

The BWG report concludes that significant amounts of public funds, both state and federal, are being used to develop herbicide-resistant crops. This conclusion was based primarily on a survey of research projects dealing with herbicide resistance in all plants, funded over the past several years. A search of the U.S. Department of Agriculture (USDA) Current Research Information System (CRIS) was used in that survey. This system contains summaries of the objectives, methods, and results of all current and recently completed agricultural research funded by USDA and states. The search by BWG yielded 409 projects related to herbicide resistance or tolerance in all plants. A subset of these projects (those funded in 1989) was used to suggest that a large amount of government funds are being used to generate herbicide-resistant crops.

We conducted a similar CRIS search in July 1990 that yielded 219 projects related to herbicide resistance in weeds and/or crops. However, close examination of the projects revealed that only 21 of the projects either had as an objective, or an accomplishment, the production of herbicide-resistant crops (Table 2.1). Almost 60

Table 2.1. Publicly-funded research to develop herbicide-resistant crops through breeding or biotechnology

Project	Herbicide[a]	Crop	Organization	State	Fund Source[b]	Method[c]
1	Acifluorfen (Blazer®)	Tomato	U IL	IL	CSRS	A
2	Acifluorfen (Blazer®)	Numerous species	Clemson U	SC	CSRS	A
2	Atrazine (Aatrex®)	Numerous species	Clemson U	SC	CSRS	A
3	Bentazon (Basagran®)	Sweet potato, peas, peppers	ARS	SC	ARS	B
4	Chlorsulfuron (Glean®)	Brassica spp.	U AZ	AZ	CSRS	B
2	Chlorsulfuron (Glean®)	Cowpea	Clemson U	SC	CSRS	A
5	Clomazone (Command®)	Tobacco	Clemson U	SC	CSRS	A
6	Glyphosate (Roundup®)	Field peas	U ID	ID	CSRS	B
7	Glyphosate (Roundup®)	Rice	Rice Exp Stn	LA	SAES	B
8	Glyphosate (Roundup®)	Alfalfa	U WY	WY	CSRS	A
9	Glyphosate (Roundup®)	Alfalfa	U NV	NV	CSRS	A, B
10	Glyphosate (Roundup®)	Poplar	USFS	WI	USFS	A
11	Haloxyfop (Verdict®)	Corn	ARS	MN	ARS	A
7	Metolachlor (Dual®)	Rice	Rice Exp Stn	LA	SAES	B
12	Metribuzin (Lexone®, Sencor®)	Potato	ARS	WA	ARS	B
13	Metribuzin (Lexone®, Sencor®)	Wheat	ARS	WA	ARS	A, B
8	Picloram (Tordon®)	Wheat	U WY	WY	CSRS	A
11, 14	Sethoxydim (Poast®)	Corn	ARS	MN	ARS	A
1	Thiadiazuron	Wheat	U IL	IL	CSRS	A
15	Not given	Peas, wheat	WA St U	WA	CSRS	A
16	Not given	Rice	ARS	AR	ARS	A
17	Not given	Legumes, cucurbits	Clemson U	SC	CSRS	A
18	Not given	Cucurbits	Penn St U	PA	CSRS	A
19	Not given	Soybeans	ARS	MN	ARS	B
20	Not given	Corn	ARS	MN	ARS	A
21	Not given	Peanut, wheat	OK St U	OK	CSRS	A

[a]Trade names are in parentheses. Some of these herbicides have several trade names. Only the most important trade names are provided.
[b]CSRS = Cooperative State Research Service, ARS = Agricultural Research Service, USFS = U.S. Forest Service, SAES = State Agricultural Experiment Station.
[c]A = biotechnology, B = conventional breeding.

such projects were listed in the BWG report. The numerical discrepancy may be due partly to misidentification of the objectives of some of the projects in the BWG report. For instance, project 20 of that report is a project identified to generate dinitroaniline-resistant carrots. In fact, this project reported the biochemical mechanism by which carrots are naturally tolerant to dinitroaniline herbicides. No part of this project has been or is planned to produce herbicide-resistant crops; however, it is possible that the information generated could be used by others to produce dinitroaniline herbicide-resistant crops. In 1990, the Agricultural Research Service (ARS) of USDA estimated that less than $100,000 of its budget was directed toward generating herbicide-resistant crops and that no projects were dedicated exclusively toward this goal.

Even though some of these projects identified by the CRIS search have listed as one of their objectives the production of herbicide-resistant crops, it is unclear what percentage of their effort is directed toward this objective. Based on titles of the papers reported by the CRIS projects that were published in scientific journals, it appears that most of the research funded by the projects has been directed toward other objectives, e.g., the study of herbicide-resistant weeds. Thus, we conclude that the amount of taxpayer funding being used for the production of herbicide-resistant crops was grossly overestimated by the BWG report.

Publicly-funded research in this area is minor in comparison with the research effort by private industry (see below). However, we have mentioned only publicly-funded research in this area in the United States. Government-funded laboratories in other industrialized countries are also carrying out this type of research (e.g., Lyon et al., 1989; Miki et al., 1990).

Should any work of this nature be publicly funded? There are minor crops for which there are no economical means of weed management. Weed management with cultural methods, including hand labor, can result in marginal profitability. There are no or few appropriate herbicides registered for these crops. The chemical industry simply cannot afford the cost of registering pesticides for crops of low dollar volume (see Chapter 4). To help producers of minor crops, USDA through its CSRS Interregional Research Project 4 (IR-4) program, headquartered at Rutgers University, assumes part of the responsibility and cost of registering herbicides for minor crops. The production of minor crops resistant to environmentally and toxicologically benign herbicides that are more effective and safer than currently used herbicides would benefit the public and the farmer.

Private Sector

Many companies that manufacture herbicides and most plant biotechnology companies have conducted research on herbicide-resistant crops. There are several reasons for this. Conferring herbicide resistance by biotechnology is generally simple compared to altering traits controlled by several genes in complicated ways that we do not understand (e.g., crop yield). Herbicide resistance can often be conferred by one gene and selection for this gene with a herbicide is easy and efficient. Also, the utility and potential value of a herbicide-resistant crop is obvious (see Chapter 4).

Since industry does not have a mandate to publish and secrecy is often important to protect a potential product, the published work on herbicide-resistant crops by industry may not represent all of their research efforts along these lines. The more publicized research and development activity in this area is presented in Table 2.2. Through such publications, the public generally becomes aware that a company is conducting research in herbicide-resistance. However, such publications are not good indicators of what specific crop the company might be targeting or how serious the company is about commercializing a herbicide-resistant crop. In fact, commercialization of several herbicide-resistant crops generated by several companies mentioned in the BWG report is not being carried out for a multitude of reasons, including economic and environmental concerns. The most notable of these is CIBA-GEIGY's decision not to commercialize triazine herbicide-resistant crops, a fact known by the BWG at the time the report was written (personal communication, Homer M. LeBaron). In addition, some of the herbicide-resistant crop research programs are being pursued as model systems to learn more about the technology or for use as selectible markers (see Chapter 3).

A good indicator of a company's intention to develop a transgenic herbicide-resistant crop is whether they have applied for an APHIS permit to field test it. In April 1991, 44 of 172 issued or pending APHIS permits for field testing transgenic organisms were for herbicide-resistant crops (personal communication, L. V. Giddings, USDA, APHIS).

The technical capacity to generate crops that are resistant to herbicides has grown tremendously over the past decade. However, simply having succeeded in conferring herbicide resistance on a crop means very little unless several other technical criteria can be met. These are discussed in the next section.

Table 2.2. Representative listing of research on development of herbicide-resistant crops by private industry

Herbicide[a]	Crop	Company	Method[b]	Strategy[c]	Reference
Atrazine (Aatrex®)	Canola	Allelix Crop Technol.	B	Site	Beversdorf et al., 1988
Bialaphos	Corn	DeKalb Plant Genetics	A	?	Giddings, 1991[d]
	Soybean	UpJohn	A	?	Giddings, 1991
Bromoxynil (Buctril®)	Tobacco	Calgene	A	Degrade	Stalker et al., 1988
	Cotton	Calgene	A	Degrade	Giddings, 1991
Glufosinate (Basta®)	Tobacco, potato, tomato	Plant Genetic Systems	A	Degrade	De Block et al., 1987 De Greef et al., 1989
	Sugarbeet, oilseed rape	Plant Genetic Systems	A	Degrade	Botterman & Leemans, 1988
	Alfalfa	Plant Genetic Systems	A	Degrade	D'Halluin et al., 1990
	Maize	DeKalb Plant Genetics	A	Degrade	Gordon-Kamm et al., 1990
Glyphosate (Roundup®)	Poplar	Calgene	A	Site	Fillatti et al., 1988
	Soybean	Monsanto Co.	A	Site	Hinchee et al., 1988
	Cotton	Monsanto Co.	A	?	Giddings, 1991
	Tomato	Monsanto Co.	A	?	Giddings, 1991
Imidazolinones	Canola	American Cyanamid/ Allelix Crop Technol.	B	?	Swanson et al., 1989
	Maize	American Cyanamid/ Plant Science Research	C	Site	Anderson & Georgeson, 1989
Sulfonylureas	Tobacco	DuPont	A	Site	Haughn et al., 1988
	Canola	Allelix Crop Technol.	C	Site	Swanson et al., 1988
	Cotton	DuPont	A	?	Giddings, 1991
2,4-D	Tobacco	Schering AG	A	Degrade	Streber & Willmitzer, 1989

[a]Trade names are in parentheses. Only the most important trade names are provided.
[b]A = gene transfer by biotechnology, B = microspore mutagenesis and selection, C = cell selection.
[c]Site = site of action, Degrade = enzyme(s) for degradation of herbicide.
[d]Giddings, L.V., 1991. List of issued and pending permits from the Biotechnology, Biologics, and Environmental Protection Division of APHIS for field tests of transgenic organisms.

Pitfalls and Successes

Insertion of foreign genes or production of mutated genes in an organism usually leads to a less fit organism from many standpoints (Haldane, 1960; Holt, 1990). For example, most of the triazine-resistant weed biotypes that have arisen from selection for mutants in the field by years of heavy triazine herbicide use are less photosynthetically efficient and less productive under most environmental conditions than the triazine-susceptible biotypes (Jursinic and Pearcy, 1988; McCloskey and Holt, 1990). The mutant gene that confers this resistance has been introduced into canola through conventional plant breeding and yields are reduced in these lines (Beversdorf et al., 1988; Darmency and Pernes, 1989). Theoretically, in certain situations, due to the low cost of atrazine, it could be agronomically advantageous to use resistant canola plus atrazine rather than higher-yielding susceptible canola (Darmency and Pernes, 1989; Forcella, 1987). However, only about 2.5 to 5% of canola (5 to 10% of *Brassica napus* and 0% *Brassica campestris*) acreage in Canada is planted with a triazine-resistant variety (personal communication, W. D. Beversdorf). Although yield loss is only 10 to 15% in triazine-resistant canola, this would translate into a significant economic loss if used on all canola acreage. This is one well-documented case of the problem of undesirable properties of introduced herbicide resistance in a crop.

In other examples of introduced resistance, there are few published data on yield in the presence and absence of the herbicide. In some cases this lack of public information suggests either that there are fitness problems of the resistant crops or that the herbicide has effects on the crops that were not anticipated when the strategy for conferring resistance was chosen. For example, the one report published on yield of glyphosate-resistant tomatoes indicates that while yields are not reduced relative to susceptible tomatoes, transgenic plants showed reduced and delayed flowering relative to unsprayed control plants

(Fraley, 1988). In some cases, published reports suggest that there are no yield penalties or other fitness problems associated with engineered resistance. Examples are crops genetically engineered or selected to be resistant to herbicides that inhibit glutamine synthetase (e.g., glufosinate or bialaphos) (De Greef et al., 1989) or acetolactate synthase (ALS) (e.g., sulfonylureas or imidazolinones) (Knowlton et al., 1988). However, more data are needed to confirm that, under a variety of field conditions, there are no undesirable secondary effects of conferring resistance to these herbicides.

Several important points should be made in this discussion.

1. Herbicide-resistant crops are not necessarily genetically superior in terms of desirable crop qualities such as yield.
2. Producing a herbicide-resistant variety of a crop that has all of the desirable properties of its susceptible counterpart is not always as simple as the popular press and, to some extent, molecular biologists have implied.
3. Even if biotechnologists are completely successful from a technical standpoint in producing a robust, herbicide-resistant crop, the engineered crop/herbicide combination must still compete economically with existing and future alternatives (see Chapter 4).

Thus, even if this technology were to be left unregulated (which is not the case), there is considerable uncertainty in many scientists' minds about its widespread adoption.

3 Potential Impacts on Weed Management, Herbicide Use Patterns, Scientific Research, and the Environment

Effects on Herbicide Use

Quantitative

Herbicides are already used on virtually every hectare of agronomic crops in this country. These are the highest dollar volume crops and, thus, pesticide companies are willing to invest large amounts of money and effort to develop and register herbicides for these crops. Thus, development of herbicide- resistant agronomic crops should have no significant effect on the percent of agronomic crops treated with herbicides. However, if a crop is engineered to be resistant to a nonselective herbicide that can be foliarly applied, the number of herbicides used on some crops can be reduced. For example, in many crops pre-emergence herbicides are used as insurance, because selective postemergence herbicides are less effective. Therefore, the farmer applies the pre-emergence herbicide without knowing the extent of the weed problem. With a crop genetically engineered to be resistant to a potent broad-spectrum, postemergence herbicide, no pre-emergence herbicide would be required and the postemergence herbicide could be applied only when needed or to only those parts of the field where needed (e.g., banded applications or spot spraying). When cost competitive, this strategy has the potential to reduce herbicide use.

If the herbicide has higher herbicidal activity per unit mass of active ingredient than that of the herbicide(s) replaced, further reductions in the quantity of herbicide used can be made. In almost every case of which we are aware, the herbicide used with the engineered crop would replace several herbicides and/or replace a herbicide with a lower activity per unit of mass. Generally, there is not a positive correlation between the mammalian toxicity (acute or chronic) of a herbicide and its herbicidal activity per unit mass.

Herbicides are used less frequently and in less total quantity on horticultural than on agronomic crops. A leading reason for this is that companies cannot afford to register many of their products for such small markets (further discussions of this topic are covered in Chapter 4). There are many existing herbicides that would be extremely valuable to farmers producing horticultural or other minor crops. However, the costs of registration preclude their use because development and registration costs may not be recovered. Producing herbicide-resistant horticultural crops may not change this substantially. In some cases, existing acceptable daily intake levels for certain herbicides and their degradation products will prevent introduction of engineered herbicide-resistant horticultural varieties (explained in Chapter 5).

Economics could also influence the impact of herbicide-resistant crops on quantity of herbicides used. Two factors are involved. First, the cost of the herbicide and its performance will determine how much of it a farmer can economically use. Second, the level of resistance of the crop will limit the amount of herbicide that can be used without crop damage. If a crop is engineered to be highly resistant to a herbicide that is or becomes very inexpensive (e.g., due to expiration of patent protection), a farmer could be tempted to use excessive amounts of the herbicide in some situations. For this reason, we recommend that, when possible, crops not be engineered to have unnecessarily high levels of resistance. However, it is important to realize that the level of resistance must be adequate to ensure the herbicide's performance under all conditions of recommended usage.

Qualitative

Herbicides vary greatly in potential toxicity to humans and wildlife, persistence in the environment, potential to enter groundwater, efficacy in killing weeds, potential to select for resistant weeds, and other factors of interest to farmers, regulatory agencies, environmentalists, and agriculturalists. Thus, there are several potential qualitative aspects of the additional herbicide option provided by herbicide-resistant crop varieties. These include weed species that are susceptible, potential environmental effects, and compatibility with other pesticides. These could be more important than the quantitative considerations in some situations and therefore should be considered separately for each herbicide. How these properties for herbicides used with genetically-engineered crops compare with those of herbicides that are currently used with the crops will depend on the crop and what herbicides are available—a constantly changing situation. The added choice could be environmentally more desirable than available herbicides. For example, a herbicide with no significant mammalian toxicity, no propensity to move to groundwater, a short half-life in the environment, and for which resistant weeds are unlikely to arise could substitute for a herbicide with less desirable attributes in any or all of these categories.

Effects on Weed Management Efficiency

The introduction of crop varieties with resistance to herbicides that could not be used previously with that crop will provide new options for farmers in designing weed management strategies. In some cases, these new options will offer better weed management at less cost. This will be especially true in situations where a foliar-applied, nonselective herbicide can be substituted for several herbicides applied at different times and by different methods. Such an option may reduce the need for tillage in weed management (see below) and the costs (both immediate and long-range) associated with it. In some cases, increased efficiency may further reduce the labor required to farm a unit of land. Unlike some other technologies (e.g., center pivot irrigation) the benefits of herbicide-resistant crops should be unrelated to farm-size.

Environmental Effects

Soil Conservation

There is growing pressure to reduce or eliminate tillage associated with weed management to reduce soil erosion and to increase soil fertility. Nonselective, foliar-applied herbicides such as glyphosate or glufosinate are ideal in no-till or minimum tillage operations. However, few crops are naturally tolerant of such herbicides. Introduction of crop varieties that are resistant to such herbicides could make conservation tillage practices highly successful in production systems in which they are not currently feasible. For example, weed pressure in some crops such as cotton in the southeastern United States is so great that conservation tillage is very difficult. A good broad-spectrum, postemergence herbicide to which cotton would be resistant would help, but none are available. For these reasons, the creation of cotton resistant to postemergence herbicides with appropriate traits could greatly enhance soil conservation in cotton production.

Groundwater Contamination

The impact of new herbicide-resistant crops on contamination of groundwater by herbicides involves many factors. These include the characteristics of both the herbicides currently used with the crop and the herbicides to which resistance is engineered. For instance, replacement of herbicides that have a relatively high potential for nonpoint source groundwater contamination (e.g., some triazines) with one that essentially does not contaminate groundwater (e.g., glyphosate) could substantially reduce the risk of groundwater contamination by herbicides. However, the opposite could occur if existing regulations did not prevent it. In most cases of which we are aware, the herbicide to which crop resistance is being engineered is not likely to contaminate groundwater significantly. Regulatory agencies should prevent the utilization of herbicide-resistant crops that would substitute a herbicide that is significantly less desirable than the herbicide(s) already used with the crops.

Also, genetically-engineered crops may allow replacement of herbicides that are used in high doses with those used at lower doses. Although low-dose herbicides, such as the sulfonylureas, have a much greater capacity per unit of active ingredient to kill susceptible plants than high-dose herbicides such as triazines, crop phytotoxicity and mammalian toxicity of the low-dose herbicides are often lower than those for the older high-dose herbicides. Lower potential toxicological effects of low-dose herbicides are due to two factors: (1) these compounds have had to pass more stringent toxicological tests than older compounds to meet registration requirements and (2) they are used in lower doses per unit area. Furthermore, in some cases, low-dose herbicides may be likely to break down more rapidly and completely by microbial action than high-dose herbicides at field use rates. For example, compare a low- and a high-dose herbicide with equal probability for degradation by soil microbes and having similar physical interactions with soils. At a high dose, microbes may break down only part of the applied herbicide before significant amounts move to greater soil depths where microbial degradation is much slower. In such cases, movement of the herbicide to groundwater may be enhanced. A low dose of a herbicide with similar characteristics should be more completely degraded before moving to greater soil depths and less (of an already lower dose) of the herbicide would be available to move to groundwater. Of course, each situation must be examined carefully because herbicides vary greatly in their interactions with soil microbes and with soil, independently of whether they are low- or high-dose herbicides.

Food Quality and Herbicide Residues

Some toxicologists have evidence that synthetic pesticide residues in our food supply currently account for significantly less than 1% of the estimated carcinogenic effects of what we eat (Ames and Gold, 1991; Ames et al., 1990), although this view is not universally accepted (Huff and Haseman, 1991). Whether development of herbicide-resistant crops will increase herbicide residues requires that each herbicide be examined individually. Current EPA regulations require residues to be determined for each new crop use (see Chapter 5). Thus, residue issues will be addressed for each herbicide-resistant crop prior to registration of the herbicide for the crop. We will provide some general examples to illustrate the complexity of this question.

For crops that are resistant through rapid metabolism of the herbicide, accumulation of the unaltered herbicide would usually not be significant. However, in these crops, conjugates or degradation products of the parent compound could accumulate. In natural tolerance, both the applied form of the herbicide and its metabolites are often altered through conjugation with natural compounds in the plant and are then compartmentalized by the plant. Breakdown of the conjugate in an animal can liberate the herbicide and its metabolites. To achieve registration of a herbicide for a particular crop, the residues of the herbicide and its major metabolites in the crop (and in meat, milk, and eggs if the crop is a feed) must be identified and quantified (see Chapter 5). Furthermore, the major identified metabolites must have passed toxicology screens. A degradation enzyme introduced from a different organism (e.g., a bacterium) may produce herbicide metabolites that were not examined during registration of the herbicide for the original intended crop. These metabolites would be identified and quantified during registration of the herbicide for the resistant crop. Any new metabolites would have to pass toxicology tests based on the same regulations used for selective herbicides.

In most cases in which resistance has been engineered by alteration of the molecular site of action, the parent compound is also metabolically degraded by the resistant plant. This situation should be treated in the same way as that of tolerance by degradation. In some cases, however, very little metabolism of the parent compound may occur in crops resistant by site-of-action changes. Under current regulation, residues will be identified in plant parts used as food or feed to determine if they exceed tolerance levels set by the EPA (see Chapter 5).

Another concern expressed by the BWG report is that transgenic crops with alien or altered genes may have their biochemistry altered in unpredictable ways, which would cause the plant to produce endogenous toxicants. This could be said for any transgenic plant, not just those engineered to be herbicide resistant. No data exist to estimate the risk of this possibility. However, guidelines for assuring the safety of foods produced by genetic modification have been developed for regulatory agencies by the International Food Biotechnology Council (International Food Biotechnology Council, 1990) and we recommend that these guidelines be followed.

There are instances in which genes have been moved from one species to another by classical breeding methods in which the new crop variety has been found to have mammalian toxicity. In the case of potato, blight resistance was introduced from a wild relative, *Solanum demissum*, to produce the variety Lenape (International Food Biotechnology Council, 1990). The new variety was quickly withdrawn when it was found that blight resistance was due to high levels of a toxic glycoalkaloid, solanine. This type of problem is more likely to arise from introduced genes that code for natural pesticides. It would be quite unlikely that genes for herbicide resistance would cause a plant to produce compounds with mammalian toxicity. Even though these possibilities have not been regulated in new crop varieties generated by traditional breeding methods, transgenic crops should be tested for alterations in nutritive value and for accumulation of toxins active in animals.

Spread of Herbicide Resistance

By Selection Among Weeds

During the past two decades the number of herbicide-resistant weed biotypes around the world has grown geometrically (Holt and LeBaron, 1990). Over 100 cases of resistance have been documented in one or more of 15 different herbicide families (Holt and LeBaron, 1990; LeBaron and McFarland, 1990). These data demonstrate the potential for weed resistance to be selected for in the field when a herbicide is used repeatedly. There is no evidence that herbicide-resistant weeds have occurred due to mutations caused by the herbicide. What little evidence exists on the origin of these resistant "biotypes" suggests they have arisen from natural mutations or from small, pre-existing subpopulations of resistant plants. The chances of resistance being selected are increased when the herbicide is persistent, is used year-after-year, and affects only one target site for which there is significant genetic plasticity. Weeds have great genetic diversity and they generally reproduce large numbers of seed per plant. These factors increase the odds of herbicide-resistance occuring and spreading rapidly. However, few of these cases have resulted in unmanageable weed problems or loss of crops because chemical and nonchemical alternatives that manage resistant plants are available for weed management in most situations (Gressel and Segel, 1990; Stephenson et al., 1990).

Regardless of whether resistant crop varieties are planted, appropriate management to prevent buildup of resistant weed populations should be practiced (Gressel and Segel, 1990; LeBaron and McFarland, 1990). Such practices as rotation of crops and herbicides, and nonchemical cultural techniques have been suggested to reduce selection pressure by herbicides. Herbicide-resistant crops may provide additional options when combined with proper management. As discussed in Chapter 2, herbicide-resistant weeds are often less fit than susceptible ones (Holt, 1990). Therefore, without the selection pressure of the herbicide, many herbicide-resistant weed biotypes would be selected against and ultimately disappear. In the case of ALS inhibitors such as sulfonylureas, continuous selection pressure by the herbicides in the field results in relatively rapid (3 to 4 years) appearance of herbicide-resistant weed biotypes (Mallory-Smith et al., 1990). If these weed biotypes are as fit as the susceptible ones from which they arose, as has been suggested in some early reports, they might be especially difficult to remove from the environment. Some companies that market ALS-inhibiting herbicides have developed specific management recommendations to avoid selection for resistant weeds in naturally tolerant crops. These recommendations would reduce the risks when genetically-engineered resistant crops are planted, as well.

By Gene Flow From Crop to Weed

As noted by others, the greatest potential risk of introducing any genetically-engineered crop variety is gene transfer from the crop to a compatible weed and its persistence in the weed population through natural selection (Goodman and Newell, 1985). The possibility of such a transfer is not unique to biotechnology, rather it is a potential problem with the introduction of any new crop variety (Goodman and Newell, 1985; Hoffman, 1990). However, in the case of genetically-engineered crops, the new genes may have been completely alien to the species before introduction. Furthermore, concomitant with genes for herbicide resistance, a selection pressure (the herbicide) is introduced that could maximize the selection for such outcrossing in the weed population. Few data are available on the extent to which crop-weed gene transfer has occurred in the past from traditional breeding. Information is available, however, on the occurrence of weedy relatives of crops, potential outcrossing rates of crops, and distances over which pollen can travel (Ellstrand and Hoffman, 1990). These data indicate that while crop-weed gene transfer is possible in some situations, theoretically it could be managed through methods that reinforce reproductive isolation of the crop (Ellstrand and Hoffman, 1990). Such techniques are already practiced by breeders who must isolate cultivars for foundation seed production. Nevertheless, this area requires further study.

Of special concern are cases in which a crop already coexists with a closely related weed with which we know the crop can interbreed. Examples are red rice in cultivated rice (both are *Oryza sativa* L.) (Langevin et al., 1990) and johnsongrass (*Sorghum halepense* [L.] Pers.) in grain sorghum (*Sorghum bicolor* [L.] Moench) (Baker, 1972). Other crops that have associated wild relatives with which they can interbreed are sugarbeets, certain cucurbits, radish, oats, and carrots (McNeill, 1976). When interspecies crosses are successful, the hybrid offspring are generally sterile. In the only report of an attempt to cross a herbicide-resistant crop with a weed, cross pollination between glufosinate-resistant canola and charlock (*Sinapis arvensis*), a closely related weed, was unsuccessful (Cherfas, 1991). Nevertheless, genetically engineering herbicide resistance into these crops should be approached with caution.

If genes conferring herbicide resistance do spread to another species as a result of outcrossing, the new genes may not spread outside the geographical and temporal regions where the herbicide is used. This is because the less fit the hybrid is, the less likely it is to persist outside the areas and times of herbicide use. Furthermore, movement of genes from a crop is likely to be much less of a problem if the genes are coded for on organellar DNA (Hauptli et al., 1985). Such genes are generally not transferred by pollen, so that the crop/weed hybrid seed could be produced only by the crop. Unfortunately, the only molecular site of action that we are aware of that is coded for by an organelle is the D-1 protein site of many of the older photosynthesis inhibitors (Duke, 1990). Inserting genes into organellar DNA for enzymes that degrade other herbicides may not be effective because the enzyme may be sequestered in the organelle and thereby rendered ineffective.

All crops are naturally tolerant to some herbicides. No cases of gene flow of the responsible gene(s) from these crops to associated weeds have been documented, despite decades of herbicide use. In fact, in virtually every known case of herbicide resistance that has originated in weeds associated with crops, the mechanism of resistance of the weed biotype has been different than the mechanism of herbicide tolerance of the associated crop. This demonstrates that weed resistance has originated independently of crop tolerance (see Chapter 2 for discussion of mechanisms of tolerance and resistance). The mechanisms of resistance in weeds that have been selected for are often the mechanisms chosen by genetic engineers to confer resistance to crops. For example, sulfonylurea herbicide-resistant weeds that have been selected for in the field, and crop plants that have been selected for in the laboratory, are both resistant due to an altered site of action (Mazur and Falco, 1989; Saari et al., 1990), even though crops for which the herbicides were developed are tolerant due to metabolic detoxification of the herbicides (Mazur and Falco, 1989). Whether genetically-engineered or -selected herbicide resistance genes in crops will more readily move to weeds than existing herbicide tolerance genes cannot be predicted with available data.

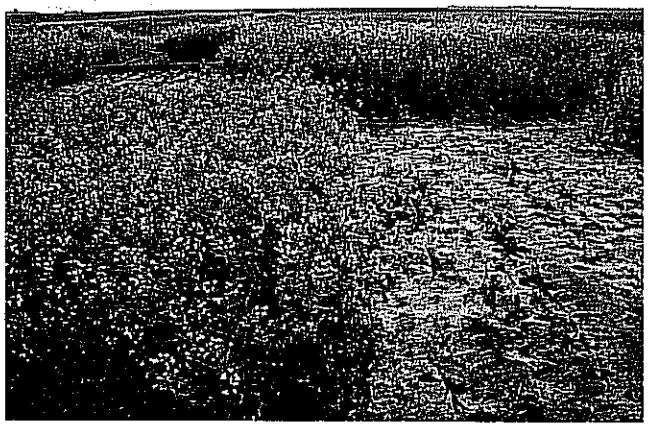

Figure 3.1. A field experiment in which sulfonylurea-resistant (left) and -susceptible (right) canola were treated postemergence with 10 g/ha of a "short residual" sulfonylurea herbicide. No phytotoxicity or yield effect of the herbicide was found, and excellent weed control was obtained. Introduction of this herbicide-resistant crop variety is not planned unless the potential of the resistant canola to become a "volunteer" weed in key rotation crops is minimized. Photograph courtesy of DuPont Agricultural Products.

Creation of New Weeds From Herbicide-Resistant Crops

Introduction of a new species into an ecosystem has severely disrupted the ecosystem in some cases. There are few cases of which we are aware in which a new crop variety has escaped from an agroecosystem to disrupt surrounding natural ecosystems. In a few cases a crop has become a weed in other crops in agroecosystems. For instance, okra has become a weed in cotton in some subtropical areas of the United States (Egley and Elmore, 1987). Several forage crops (e.g., bermuda grass) are also weeds. One potential difficulty of herbicide-resistant crops would be their control when growing as a volunteer plant within a rotation crop. For example, corn made resistant to aryloxyphenoxypropionates or cyclohexanediones would eliminate the use of these herbicides in controlling volunteer corn in soybean fields. However, alternatives are available, such as rope wick application of glyphosate. Volunteer canola can also be a "weed" problem in rotation crops of corn, wheat, sugarbeets, and soybeans. Unless this potential problem can be solved, DuPont does not plan to commercialize its currently available sulfonylurea-resistant canola (Figure 3.1), even though the resistant crop appears to be a technical success.

There is some concern that transgenic crops could themselves escape to become serious pests or displace other species in natural ecosystems. We view this as highly unlikely. Cultivated crops generally will not survive and reproduce without human efforts to prevent competition from other species, to relieve other pest pressures, and to provide more nutrients and water than would normally be available. A gene for herbicide resistance would not change this and, as mentioned earlier, such genes may reduce the ability to compete with other species. Studies with glufosinate-resistant oil seed-canola demonstrate that the plants do not reproduce in the absence of cultivation to relieve competition (Cherfas, 1991). There are no reasons of which we are aware to suspect that different results would be obtained with other species or with resistance to other herbicides.

Scientific and Technological Spinoff

Several important tools in biotechnology and molecular genetics have been improved or originated from research on herbicide-resistant crops. For example, selectible markers are traits that, when transferred into an organism by recombinant DNA techniques, provide the researcher with a tool for identifying and isolating successful transformants. Before herbicide resistance markers were available, most molecular biologists used antibiotic resistance as a selectible marker. Herbicide resistance is now used by many molecular biologists as a selectible marker because it is highly effective and is significantly less expensive to use than antibiotic resistance. Research with herbicide-resistant tissue cultures of crops has also been a principal driving force to develop new plant regeneration techniques.

Another significant application of herbicide resistance could be its use as a dominant selectible marker for classical breeding purposes. The resistance genes can be physically linked to other genes conferring agronomically useful traits that are not easy to monitor (e.g., Figure 3.2).

Figure 3.2. Use of a herbicide (glufosinate) resistance marker linked to a gene designed for dominant male sterility. Both resistant (left) and susceptible (right) oilseed rape plants were treated with glufosinate. The availability of linked herbicide resistance in this crop allows the maintenance and multiplication of the male sterile line after backcrossing with the parental line. Photograph courtesy of Plant Genetic Systems, N.V.

Research into the physiological and biochemical mechanisms of resistance or tolerance to herbicides has led to important discoveries in understanding fundamental plant processes. For instance, much of what we know of photosynthetic electron transport was facilitated by studies of mutant weeds and algae that have resistance to herbicides that inhibit photosynthetic electron transport. This work led to the discovery of the function of certain chloroplast proteins (Steinback et al., 1981) and to their structural elucidation—work that eventually led to a Nobel prize (Deisenhofer et al., 1985).

Much of what we know of the shikimate pathway in plants (most of the carbon dioxide fixed by terrestrial plants flows through this pathway) is due to work on the herbicide glyphosate and resistance to glyphosate. Better understanding of the shikimate pathway has the potential to improve several aspects of plant protection and plant productivity. For example, understanding the regulation of this pathway could provide plant scientists the capability of manipulating the pathway, either genetically or chemically, to maximize carbon flow into harvested components of a crop.

Research with herbicide-resistant plants has been important in demonstrating the molecular mechanism of herbicide action. The most unequivocal proof that a herbicide kills plants by affecting a single molecular site is to generate a resistant plant by manipulation of only the gene that codes for that site. The controversy regarding the mechanism of action of the aryloxyphenoxypropionate and the cyclohexanedione herbicides was resolved by generation of resistant plants by selection for resistant acetyl-CoA carboxylase (Parker et al., 1990). Previously, others had postulated another site of action (the plasmalemma) that might have had mammalian health implications. These examples of scientific spinoff from herbicide resistance research are but a few of many advances in plant science facilitated by or due entirely to research in this area. Thus, this type of research warrants continued public funding to enhance plant science in the United States. Research on herbicide resistance funded by foreign governments will undoubtedly continue.

4 Economics of Herbicide-Resistant Crops

The herbicide and seed markets have become replacement markets; i.e., new sales are generated by replacing a currently used product. In a replacement market the most important factor with regard to success of any new technology, including herbicide-resistant crops, is the competitive advantage provided. If there is a large perceived competitive advantage, there will be a high level of interest in developing the technology. Conversely, a small perceived competitive advantage will result in low interest. Based on competitive advantage, there should be a niche for herbicide-resistance technology in agriculture, particularly in minor crops. However, as will become clear in this section, herbicide-resistant crops will not "revolutionize" agriculture.

One of the most important factors in considering the need, and thus, the success, of herbicide-resistant crops is the availability of alternative herbicides. In major crops, particularly corn and soybeans, there are multitudes of excellent herbicides for management of virtually all broadleaf and grass weeds that are of significant economic importance. New herbicides that are more effective and more environmentally sound are continuously being introduced. To date, selectivity exists for corn and soybean herbicides; thus, introducing a herbicide resistance trait is not necessary to fill a general weed management need. Furthermore, the cost of controlling a common spectrum of weeds in major agronomic crops is relatively low (approximately $15 per acre in 1990). Thus, it will be difficult for herbicide-resistant crop technology to be economically competitive in these markets. To be competitive, the cost of the herbicide used in crops made resistant to that herbicide will have to be equal to or less expensive than available alternatives. However, part or all of the cost saving for the herbicide, if less expensive, may be consumed by an increased price for seed.

One potential fit for herbicide resistance in major agronomic crops is management of specific weed problems not well managed by available herbicides. Two assumptions are necessary for this use to be applicable: (1) the herbicide must effectively manage the weed and (2) a more effective herbicide for the weed will not be introduced into the market. Other possible advantages of herbicide-resistant crops are replacement of several herbicides by one herbicide, replacement of a high-dose herbicide with a low-dose herbicide, or replacement of pre-emergence herbicides with postemergence herbicides. The first two of these advantages would result in a decrease in the overall herbicide load in the environment. Furthermore, in any of these cases, there could be an economic advantage to the farmer. Herbicide-resistant crops with a low level of resistance (e.g., 10-fold) to a herbicide could replace crops with an even lower level of tolerance (e.g., 2- to 4-fold) to the same herbicide. This would eliminate the occasional crop injury caused by unpredictable interactions of environmental, chemical, and application factors (e.g., overlapping spray patterns). This type of enhanced selectivity is being pursued by at least one herbicide manufacturer. Finally, the long-term advantage of a herbicide-resistant crop allowing the farmer to switch to a more environmentally benign herbicide should be considered.

There is a useful fit for developing herbicide resistance in minor crops, such as vegetables. Because of the small market size and large cost associated with obtaining a government registration for use (see Chapter 5), no herbicides have been developed exclusively for a particular minor crop. If a herbicide becomes registered for a major crop, the potential for use in minor crops can then be assessed. However, inherent tolerance of these crops to herbicides developed for major crops is often not adequate. Therefore, low cost herbicides for weed management in many minor crops are not available, resulting in generally higher weed management costs per acre in minor crops than in agronomic crops. For example, weed management (with herbicides, cultivation, and hand weeding) in California lettuce fields averaged $104 to $166 per acre from 1983 to 1987[a]. Clearly, development of herbicide-resistant minor crops could be of significant economic benefit to farmers growing these crops.

As stated above, the interest of the private sector in herbicide-resistant crops will be driven primarily by

[a]Data assembled by D. Bodnar, Marketing Research Department, Sandoz Crop Protection Corporation.

potential economic benefit to the company involved in this technology. Two different segments of the private sector will need to be involved for commercial introduction to be achieved. These are companies that produce herbicides and companies that supply seeds of herbicide-resistant crops. Unless both groups obtain an economic benefit from herbicide resistance, this technology will fail if left entirely to the private sector. Even in situations where chemical companies and seed companies are owned by a single parent company, there will need to be economic benefits to both groups before herbicide- resistant crop technology will be considered a success. The factors to consider for economic success of the herbicide and the seed supplier are different, so these will be discussed separately. Where herbicide resistance is thought to be a viable business venture, the final and perhaps most important consideration is farmer acceptance of this new technology.

Seed Supplier

There are two primary driving forces for a seed company to develop seeds of herbicide-resistant crops. The first, an economic one, has two potential benefits: (1) an increased price per unit of seed and (2) an increased market share for that seed. The business of selling seeds to farmers is very competitive and, thus, an increase in price will be possible only if the farmer can identify a significant benefit for paying the extra price. In fact, often the economic "3 to 1 rule" is used as an initial estimate of the success of a price increase. This "rule" is that for the farmer to pay a $1 increase in cost, there should be a $3 benefit or savings to the farmer. Because of the high value of many minor crops and a general lack of inexpensive weed management in these crops, there may be a clear economic benefit to the farmer to use seed of herbicide-resistant minor crops. Although there will be a significant potential for increased market share when a seed company can offer herbicide-resistant seeds, the increased share may erode when resistant seeds become available from competitors.

A second driving force for a seed company to offer herbicide resistance in a crop variety is defensive. In other words, "if our competitors offer herbicide-resistant seed, then we must also offer it." Because the seed business is very competitive, a small advantage of one seed type over another can result in substantial shifts in market share. Thus, seed companies may feel compelled to explore this technology to prevent being shut out of a potential market.

Developing herbicide resistance in a given crop is expensive and time consuming for research groups. Therefore, the choice of crops in which to develop herbicide resistance is a significant question for seed companies having this capability. After the herbicide resistance has been successfully engineered into the crop of choice (which may take two to four years to achieve), there will usually be the need for a multiple year backcross breeding program to introduce the trait into the best available varieties. After the backcross program, a two to four year field performance testing program is required, both internal and external to the company. If this phase is successful, there is a seed increase period of one to two years to produce adequate seed for market introduction. Thus, a minimum of five to six years will be needed to introduce a single herbicide resistance trait and marketing of a commercially available seed could take more than ten years.

A consideration in determining which crops to make resistant is the potential for proprietary protection of the technology once research and development are completed. The most desirable seeds for herbicide resistance are those that are sold as proprietary hybrids. In contrast, the seeds from open-pollinated crops can be saved by the farmer for planting the following season. Furthermore, the U.S. Plant Variety Protection Act contains a research clause whereby varieties protected under this act can be used by plant breeders as sources for developing new varieties. This research clause is often called the "Plant Breeders' Right" and provides a mechanism for moving traits between varieties, even though they are owned by different companies. Patenting the herbicide-resistant variety is the more restrictive alternative to marketing proprietary hybrids; however, it provides the best protection. A second consideration in deciding which crops to make resistant is the ability of the seed to withstand a price increase. If a price increase cannot take place, the seed company must rely on increased market share to cover the cost of developing a herbicide-resistant seed line.

Companies becoming involved in selling seeds of herbicide-resistant varieties will generate additional inventory that must be managed. Many crops are currently available in numerous varieties and as multiple maturity zone types (e.g., field corn and soybeans). Therefore, the required inventory is currently large and adding herbicide resistance will result in a further increase in the diversity of inventory that must be carried. Not only will resistant and non-resistant seed need to be available for each variety and each maturity zone, but in many crops more than one type of herbicide resistance technology might be available.

Herbicide Supplier

As with the seed supplier, the driving force for a herbicide manufacturer to become involved in a herbicide-resistant crop program is primarily economic. While the herbicide manufacturer will realize a profit from additional sales, there is a need for significant investment prior to selling the additional herbicide. The herbicide must first be registered for the herbicide-resistant crop (see Chapter 5). This requires conducting residue and metabolism studies, possibly involving isolation and identification of new metabolites and toxicology studies—a time-consuming and costly process.

The supplier must also consider the market impact of new herbicides that would be competitive with those herbicides being sold in association with resistant seeds. The risk is greatest for the major crops because these crops are targeted for the greatest influx of new herbicides. For example, corn varieties resistant to a particular herbicide class (imidazolinones) are currently being developed (Table 2.2). However, there are now herbicides with a similar mode of action (sulfonylureas) being registered for use in corn to which corn is naturally tolerant. The risk of competing herbicides being introduced into the market is least for minor crops, for which new herbicides are introduced only occasionally. The problem with minor crops is that the herbicide sales potential in those crops is substantially less than in the major crops, even though the registration cost can be approximately equal.

Thus, the incentive for herbicide suppliers to increase sales of currently registered herbicides by supporting development of herbicide-resistant crops is not particularly high. Exceptions are herbicides that have no crop selectivity (e.g., glyphosate and glufosinate). Developing crops resistant to these herbicides can create entirely new markets. But once the patent has expired for such herbicides, the first manufacturer must share the market with other companies that choose to produce the same herbicide, provided the other companies pay the cost of generating registration data.

The impact of developing herbicide-resistant crops on the spread of weed resistance (Chapter 3) is of significant concern to most herbicide suppliers. This is certainly a factor that must be considered by the herbicide supplier when deciding whether or not to support the development of herbicide-resistant crops for their proprietary herbicide(s). If introducing herbicide-resistant crops significantly increases the chances for selection of herbicide resistance in weeds, the supplier should not risk introducing this trait in crops. Increased weed resistance to the herbicide could reduce the long-term profitability for that herbicide.

Farmer Acceptance

Farmers producing major crops such as corn and soybeans employ a wide range of weed management strategies. It may be difficult to convince these farmers to purchase a herbicide-resistant seed plus herbicide package unless there is a clear advantage or need for the package. The advantages could be reduced total price for weed management or an improved spectrum of weeds controlled, particularly if there is a need to manage difficult weeds. For minor crops such as many vegetable crops, there may be a significant cost saving to the farmer by using a herbicide-resistant variety with the corresponding herbicide.

In major crops there are numerous weed management alternatives and in nearly all minor crops there are at least some management options available. Therefore, in few or no cases will herbicide resistance be the only, or even the major, trait considered by farmers in selecting seed. Thus, it will be an important requirement that herbicide-resistant varieties produce a product of the same quality and quantity as nonherbicide-resistant varieties. This is particularly critical for vegetable crops where quality and quantity of the crop are both critical factors in variety selection by farmers. If the herbicide-resistant trait is not available in the most advanced seed lines, or if the trait secondarily affects crop quality, the technology will not be adopted by farmers.

In summary, herbicide-resistant crop varieties produced by any method will not be extensively used unless there are clear advantages to the farmer. As pointed out earlier, simply because something is technically feasible does not assure its adoption. Many factors could prevent the economic viability of herbicide-resistant crop varieties. These include cost of the herbicide, efficacy of the herbicide on the weeds associated with the crop, cost of the seed of the new variety, and quality and productivity of the new variety. For any herbicide-resistant crop developed, these factors could combine to save the farmer significant cost for weed management or they could prohibit its use.

Consumer Acceptance

Genetically-engineered organisms, especially food crops, have received a wide range of negative publicity. Despite safety assurances of regulatory agencies, public acceptance of herbicide-resistant crops could be adversely affected by such publicity. If so, this factor could play an important role in the economic success or failure of herbicide-resistant crops. Public opinion is a variable that can fluctuate considerably with time and between different geographic areas. The adverse publicity generated by misuse of one herbicide-resistant crop could hamper utilization of other herbicide-resistant crops. For this reason, we urge that those engaged in the development of herbicide-resistant crops use a high degree of caution and good judgement in choosing herbicide/crop combinations and in all aspects of development and testing.

Overall Economic Effects

What would be the overall economic effects of introducing herbicide-resistant crops if one assumes that the technology will be readily adopted by the agrichemical industry, the seed companies, the public, and farmers? Only very imprecise estimates, based on assumptions, can be made. Nevertheless, using an economic model, Tauer and Love (1989) have generated economic predictions of the effect of adoption of herbicide-resistant corn in the United States. An assumption underlying the model was that this new technology would be accepted and utilized rapidly by farmers because of clear improvements in production efficiency. In short, their model predicted the following:

1. Farmers in areas with relatively low weed pressure would at first benefit economically, provided they were the first to utilize the new technology, but they would later lose as corn prices fell due to improved production everywhere.
2. Farmers in areas of high weed pressure would benefit economically at all times after adoption.
3. Consumers would benefit due to decreased food costs.
4. The economic benefit to consumers would be of greater magnitude than the overall eventual losses to farmers.
5. Eventually, the new technology would increase acreage of corn in high weed pressure areas and decrease it in areas of low weed pressure, such as the current corn belt.

In summary, the authors concluded that even with widespread adoption, this new technology would result in only small total changes in acreages and net farm income. It must be emphasized that many factors other than those considered in this model might affect the overall economic impact of the introduction of herbicide-resistant crops. Also, the assumption made in this model that this technology will be rapidly adopted is questionable.

Nevertheless, as with any new technology, the analysis by Tauer and Love (1989) points out the potential for many possible effects of herbicide-resistant crops. There could be some short-term or even long-term economic costs associated with the widespread adoption of such technology. However, any increase in U.S. agricultural production efficiency will probably benefit the U.S. consumer and the U.S. economy. If there is a clear economic advantage to this technology, those countries that utilize it first will benefit the most.

5 Regulation of the Technology

The BWG report raised concerns regarding food and environmental safety and the need for additional government regulation of herbicide-resistant crops. This technology is already being regulated by two federal agencies, the EPA through the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and USDA Animal and Plant Health Inspection Service (APHIS) through the Plant Pest Act. The use of a herbicide on any crop (including crops made herbicide-resistant by genetic engineering) requires EPA registration of the herbicide on that crop. A primary purpose of the EPA requirement for registration for herbicide use on each crop is to set standards for monitoring cumulative residues of the herbicide and its metabolites and to set acceptable tolerance levels for safe consumption. In addition, approval from state regulatory agencies is required for herbicide use. Requirements for state approval vary among states. The current procedures that must be followed prior to U.S. herbicide registration on a particular crop are reviewed briefly below.

The use of a herbicide on a herbicide-resistant crop would, in most cases, constitute a new use of the herbicide and would require a modification of the herbicide label under FIFRA. For each crop where registration is desired, the metabolic degradation of the parent herbicide in that crop must be determined. Metabolic degradation studies are accomplished by treating the crop plant with radioactive herbicide and then, over time, analyzing radioactive compounds. At least 80% of the radioactivity has to be characterized and all individual metabolites representing more than 0.01 part per million (ppm) must be identified. The chemical pathway for arriving at these metabolites also must be determined. However, if three related crops (e.g., three cucurbits) have been registered and the metabolism patterns are the same for each crop, then further metabolism studies for similar crops are usually not required by the EPA for registration.

After the metabolism studies are complete, analytical methods must be developed to quantify each of the metabolites and the parent herbicide so that the residue levels of each can be determined in any crop for which a labelled use is being requested. Using these analytical methods, the residue levels of the herbicide and its degradation products (metabolites) must be determined in a crop treated with the herbicide. If the crop sometimes is processed prior to consumption, then the residue levels also must be determined in the processed form of the crop. Residue levels in animal products also must be determined if the crop is used as feed for livestock. If significant levels of residue occur in the crop (greater than 0.01 ppm) and the crop sometimes is used as animal feed, large animal and poultry metabolism studies must be conducted and appropriate analytical methods developed to identify the parent herbicide and individual metabolites. Then residue studies in animals, using treated crops as feed, must be conducted to determine residue levels in meat, milk, and eggs. Regardless of how many crops are registered for use of a particular herbicide, the residue assessment must be completed for each crop. Based on the residues found in the crop being assessed, the EPA sets a "tolerance" residue level for the parent herbicide plus all identified metabolites in that crop.

In addition to the tolerance level, the EPA sets a maximum Acceptable Daily Intake (ADI) level (now usually called Reference Dose) for each herbicide based on the toxicology profile obtained during the original herbicide registration. The ADI is a part per million value based on taking the lowest no-effect level from critical animal toxicology studies and assigning a safety factor of 100-fold. Furthermore, it is assumed that all of the crop is treated with the herbicide and that all of the crop contains the maximum allowable residue levels (the tolerance levels) of both the herbicide and its degradation products. The portion of the ADI that each crop represents is determined by an EPA computer program that models the dietary intake for each segment of the human population. The more a particular food is consumed, the greater percentage of the ADI is assigned to that crop. Once the cumulative tolerances for all crops on which a particular herbicide is registered reach 100% of the ADI, no new crops can be added to the registration for that herbicide unless an existing registration is canceled to reduce the cumulative tolerances below the ADI.

The setting of the tolerance residue level for each crop and the ADI level for each herbicide by the EPA provides excellent food safety for the consumer.

Herbicides used on crops made resistant by genetic engineering will be registered by the above procedures under FIFRA. Therefore, additional regulations for resistant crops should not be required.

The FDA is mandated by the U.S. Congress to regulate food quality and to insure that neither agricultural commodities nor consumable processed derivatives of those commodities contain toxicologically significant levels of naturally-occurring toxicants or food additives. The IFBC has proposed that the regulation of genetically-modified food plants derived by nontraditional genetic modification be patterned directly on existing law and practice (International Food Biotechnology Council, 1990). If the result of the genetic modification is the introduction of a chemical entity, which if introduced exogenously would be regulated as a food additive or generally recognized as safe (GRAS) substance, it would be regulated in the genetically-modified plant as a food additive or GRAS substance. If the purpose of the genetic modification is to affect an agronomic function (e.g., herbicide resistance), the plant would be regulated as foods are now, under Section 402(a)(1) of the Federal Food, Drug, and Cosmetic Act. We endorse these recommendations of the IFBC.

Under authority of the Plant Pest Act, APHIS regulates genetically-engineered plants, including those made herbicide-resistant by this technology. The altered plants are considered pests until proven otherwise. Verification of safety is accomplished by field testing, which requires an APHIS permit. These tests include yield trials, demonstration of management by other herbicides, and demonstration that herbicide resistance is not transferred to other plants by natural means. Only after passing these tests would the herbicide-resistant crops be approved for use. After the herbicide-resistant crop is shown to be safe in the environment and not a pest, a petition must be filed to remove the crop from the list of regulated pests.

The combination of herbicide regulation by the EPA, herbicide-resistant crop regulation by USDA-APHIS, and regulation of foods from genetically-engineered crops by FDA, along with state regulation, should be sufficient to ensure both consumer and environmental safety. Substantial additional regulation would serve only to add redundancy to the system and to slow the realization of potential benefits to be derived from herbicide-resistant crops.

6 Recommendations

A difficulty in making encompassing recommendations is that the situation is as complex as are the many crops, herbicides to which crops can be engineered for resistance, currently available herbicides for those crops, future alternatives to herbicides for weed management in those crops, and the economic and environmental considerations of each factor. For these reasons, our most important recommendation is that each situation must be examined in the context of all pertinent factors. Although political and various advocacy organizations would like to see broad conclusions regarding this topic, sweeping generalizations cannot be made in such a complex area. Nevertheless, a few specific recommendations can be made:

- When possible, unnecessarily high levels of resistance should not be genetically engineered into crops.
- Funding of scientific research on herbicide resistance and herbicide tolerance should not be restricted by legislation.
- Crop resistance to environmentally suspect herbicides should not be produced for commercialization by biotechnology.
- Crops with associated weeds with which they freely interbreed should not be made resistant to herbicides by biotechnology without also introducing genetic barriers to outcrossing.
- Introduction of herbicide-resistant crops should be accompanied by recommendations to prevent selection and spread of weed resistance. A complete weed management system should accompany the use of herbicide-resistant crops.
- The International Food Biotechnology Council's (IFBC) guidelines for transgenic food crops should be followed with herbicide-resistant crops.

Literature Cited

Ames, B. N. and L. S. Gold. 1991. Cancer prevention strategies greatly exaggerate risks. *Chem. Eng. News* 69:28-32.

Ames, B. N., M. Profet, and L. S. Gold. 1990. Dietary pesticides (99.99% all natural). *Proc. Natl. Acad. Sci. USA* 87:7777-7781.

Anderson, P. C. and M. Georgeson. 1989. Herbicide-tolerant mutants of corn. *Genome* 31:994-999.

Austin, S. and J. P. Helgeson. 1987. Interspecific somatic fusions between *Solanum brevidens* and *S. tuberosum*. *Plant Mol. Biol.* 140:209-222.

Baker, H. G. 1972. Migrations of weeds. Pp. 327-347. In D. H. Valentine (Ed.). *Taxonomy, Phytogeography and Evolution*. Academic Press, London and New York.

Beversdorf, W. D., D. J. Hume, and M. J. Donnelly-Vanderloo. 1988. Agronomic performance of triazine-resistant and susceptible reciprocal spring canola hybrids. *Crop Sci.* 28:932-934.

Botterman, J. and J. Leemans. 1988. Engineering herbicide resistance into plants. *Trends in Genet.* 4:219-222.

Council for Agricultural Science and Technology. 1990. *Alternative Agriculture: Scientists' Review*. Special Publication No. 16. Ames, Iowa. 182 pp.

Chaleff, R. S. and T. B. Ray. 1984. Herbicide-resistant mutants from tobacco cell cultures. *Science* 223:1148-1152.

Cherfas, J. 1991. Transgenic crops get a test in the wild. *Science* 251:878.

Darmency, H. and J. Pernes. 1989. Agronomic performance of a triazine resistant foxtail millet (*Setaria italica* [L.] Beauv.). *Weed Res.* 29:147-150.

De Block, M., J. Botterman, M. Vandewiele, J. Dockx, C. Thoen, V. Gosselé, N. Movva, C. Thompson, M. Van Montagu, and J. Leeman. 1987. Engineering herbicide resistance in plants by expression of a detoxifying enzyme. *EMBO J.* 6:2513-2518.

De Greef, W., R. Delon, M. De Block, J. Leemans, and J. Botterman. 1989. Evaluation of herbicide resistance in transgenic crops under field conditions. *Bio/Technol.* 7:61-64.

Deisenhofer, J., O. Epp, K. Miki, R. Huber, and H. Michel. 1985. Structure of the protein subunits in the photosynthetic reaction center of *Rhodopseudomonas viridis* at 3 Å resolution. *Nature (London)* 318:618-624.

D'Halluin, K., J. Botterman, and W. De Greef. 1990. Engineering of herbicide-resistant alfalfa and evaluation under field conditions. *Crop Sci.* 30:866-871.

Duke, S. O. 1990. Overview of herbicide mechanisms of action. *Environ. Health Perspect.* 87:263-271.

Egley, G. H. and C. D. Elmore. 1987. Germination and the potential persistence of weedy and domestic okra (*Abelmoschus esculentus*) seeds. *Weed Sci.* 35:45-51.

Ellstrand, N. C. and C. A. Hoffman. 1990. Hybridization as an avenue of escape for engineered genes. *BioSci.* 40:438-442.

Fillatti, J. J., B. Haissig, B. McCown, L. Comai, and D. Riemenschneider. 1988. Development of glyphosate-tolerant *Populus* plants through expression of a mutant *aroA* gene from *Salmonella typhimurium*. Pp. 243-249. In J. W. Hanover and D. E. Keathley, (Eds.). *Genetic Manipulation of Woody Plants*. Plenum, New York.

Forcella, F. 1987. Herbicide-resistant crops: Yield penalties and weed thresholds for oilseed rape (*Brassica napus* L.). *Weed Res.* 27:31-34.

Foy, C. L. 1964. Volatility and tracer studies with alkylamino-s-triazines. *Weeds* 12:103-108.

Fraley, R. T. 1988. Field testing genetically engineered plants. Pp. 83-86. In R. T. Fraley and J. Schell (Eds.). *Genetic Improvements of Agriculturally Important Crops. Progress and Issues. Current Communications in Molecular Biology*. Cold Spring Harbor Laboratory, New York.

Fuerst, E. P., H. Y. Nakatani, A. D. Dodge, D. Penner, and C. J. Arntzen. 1985. Paraquat resistance in *Conyza*. *Plant Physiol.* 77:984-989.

Goldsbrough, P. B., E. M. Hatch, B. Huang, W. G. Kosinski, W. E. Dyer, K. M. Herrmann, and S. C. Weller. 1990. Gene amplification in glyphosate tolerant tobacco cells. *Plant Sci.* 72:53-62.

Goldburg, R., J. Rissler, H. Shand, and C. Hassebrook. 1990. *Biotechnology's Bitter Harvest*. Biotechnology Working Group. 73 pp.

Goodman, R. M. and N. Newell. 1985. Genetic engineering of plants for herbicide resistance: Status and prospects. Pp. 47-53. In H. O. Halvorson, D. Pramer, and M. Rogul (Eds.). *Engineered Organisms in the Environment: Scientific Issues*. Amer. Soc. Microbiol., Washington, D.C.

Gordon-Kamm, W. J., T. M. Spencer, M. L. Mangano, T. R. Adams, R. J. Daines, W. G. Start, J. V. O'Brien, S. A. Chambers, W. R. Adams, Jr., N. G. Willetts, T. B. Rice, C. J. Mackey, R. W. Krueger, A. P. Kausch, and P. G. Lemaux. 1990. Transformation of maize cells and regeneration of fertile transgenic plants. *The Plant Cell* 2:603-618.

Gressel, J. and L. A. Segel. 1990. Herbicide rotations and mixtures. Effective strategies to delay resistance. *Amer. Chem. Soc. Symp. Ser.* 421:430-458.

Haldane, J. B. S. 1960. More precise expressions for the cost of natural selection. *J. Genet.* 57:351-360.

Haughn, G. W., J. Smith, B. Mazur, and C. Somerville. 1988. Transformation with a mutant *Arabidopsis* acetolactate synthase gene renders tobacco resistant to sulfonylurea herbicides. *Mol. Gen. Genet.* 211:266-271.

Hauptli, H., N. Newell, and R. M. Goodman. 1985. Genetically engineered plants: Environmental issues. *Bio/Technol.* 3:437-442.

Hinchee, M. A. W., D. V. Conner-Ward, C. A. Newell, R. E. McDonnell, S. J. Sato, C. S. Gasser, D. A. Fischhoff, D. B. Re, R. T. Fraley, and R. B. Horsch. 1988. Production of transgenic soybean plants using *Agrobacterium*-mediated DNA transfer. *Bio/Technol.* 6:915-922.

Hoffman, C. A. 1990. Ecological risks of genetic engineering of crop plants. *BioSci.* 40:434-437.

Holt, J. S. 1990. Fitness and ecological adaptability of herbicide-resistant biotypes. *Amer. Chem. Soc. Symp. Ser.* 421:419-429.

Holt, J. S. and H. M. LeBaron. 1990. Significance and distribution of herbicide resistance. *Weed Technol.* 4:141-149.

Huff, J. E. and J. K. Haseman. 1991. Exposure to certain pesticides may pose real carcinogenic risk. *Chem. Eng. News* 69:33-37.

International Food Biotechnology Council. 1990. Biotechnologies and food: Assuring the safety of foods produced by genetic modification. *Regul. Toxicol. Pharmacol.* 12:i-S196.

Jursinic, P. A. and R. W. Pearcy. 1988. Determination of the rate limiting step for photosynthesis in isonuclear rape seed (*Brassica napus* L.) biotypes resistant to atrazine. *Plant Physiol.* 88:1195-1200.

Knowlton, S., B. J. Mazur, and C. J. Arntzen. 1988. Creation and field testing of sulfonylurea- resistant crops. Pp. 55-60. In R. T. Fraley, N. M. Frey, and J. Schell (Eds.). *Genetic Improvements of Agriculturally Important Crops. Progress and Issues. Current Communications in Molecular Biology,* Cold Spring Harbor Laboratory, New York.

Langevin, S. A., K. Clay, and J. B. Grace. 1990. The incidence and effects of hybridization between cultivated rice and its related weed red rice (*Oryza sativa* L.). *Evolution* 44:1000- 1008.

LeBaron, H. M. and J. McFarland. 1990. Herbicide resistance in weeds and crops. An overview and prognosis. *Amer Chem. Soc. Symp. Ser.* 421:336-352.

Lee, K. Y., J. Townsend, J. Tepperman, M. Black, C. F. Chui, B. Mazur, P. Dunsmuir, and J. Bedbrook. 1988. The molecular basis of sulfonylurea herbicide resistance in tobacco. *EMBO* 7:1241-1248.

Lichtenthaler, H. K. 1990. Mode of action of herbicides affecting acetyl-CoA carboxylase and fatty acid biosynthesis. *Z. Naturforsch.* 45c:521-528.

Lyon, B. R., D. J. Llewellyn, J. L. Huppatz, E. S. Dennis, and W. J. Peacock. 1989. Expression of a bacterial gene in transgenic tobacco plants confers resistance to the herbicide 2,4- dichlorophenoxyacetic acid. *Plant Molec. Biol.* 13:533-540.

Mallory-Smith, C. B., D. C. Thill, and M. J. Dial. 1990. Identification of sulfonylurea herbicide- resistant prickly lettuce (*Lactuca serriola*). *Weed Technol.* 4:163-168.

Mazur, B. J. and S. C. Falco. 1989. The development of herbicide resistant crops. *Annu. Rev. Plant Physiol. Plant Mol. Biol.* 40:441-470.

McCloskey, W. B. and J. S. Holt. 1990. Triazine resistance in *Senecio vulgaris* parental and nearly isonuclear backcrossed biotypes is correlated with reduced productivity. *Plant Physiol.* 92:954-962.

McNeill, J. 1976. The taxonomy and evolution of weeds. *Weed Res.* 16:399-413.

Miki, B. L., H. Labbé, J. Hattori, T. Ouellet, J. Gabard, G. Sunohara, P. J. Charest, and V. N. Iyer. 1990. Transformation of *Brassica napus* canola cultivars with *Arabidopsis thaliana* acetohydroxyacid synthase genes and analysis of herbicide resistance. *Theor. Appl. Genet.* 80:449-458.

Parker, W. B., L. C. Marshall, J. D. Burton, D. A. Somers, D. L. Wyse, J. W. Gronwald, and B. G. Gengenbach. 1990. Dominant mutations causing alterations in acetyl-coenzyme A carboxylase confer tolerance to cyclohexanedione and aryloxyphenoxypropionate herbicides in maize. *Proc. Natl. Acad. Sci. USA* 87:7175-7179.

Quinn, J. P. 1990. Evolving strategies for the genetic engineering of herbicide resistance in plants. *Biotech. Adv.* 8:321-333.

Saari, L. L., J. C. Cotterman, and M. M. Primiani. 1990. Mechanism of sulfonylurea herbicide resistance in the broadleaf weed, *Kochia scoparia. Plant Physiol.* 93:55-61.

Stalker, D. M. and K. E. McBride. 1987. Cloning and expression in *Escherichia coli* of a *Klebsiella ozaenae* plasmid-borne gene encoding a nitrilase specific for the herbicide bromoxynil. *J. Bacteriol.* 169:955-960.

Stalker, D. M., K. E. McBride, and L. D. Malyj. 1988. Herbicide resistance in transgenic plants expressing bacterial detoxification genes. *Science* 242:419-423.

Steinback, K. E., L. McIntosh, L. Bogorad, and C. J. Arntzen. 1981. Identification of the triazine receptor protein as a chloroplast gene product. *Proc. Natl. Acad. Sci. USA* 78:7463-7467.

Steinrücken, H. C., A. Schulz, N. Amrhein, C. A. Porter, and R. T. Fraley. 1986. Overproduction of a 5-enol-pyruvylshikimate-3-phosphate synthase in a glyphosate-tolerant Petunia hybrid cell line. *Arch. Biochem. Biophys.* 244:169-178.

Stephenson, G. R., M. D. Dykstra, R. D. McLaren, and A. S. Hamill. 1990. Agronomic practices influencing triazine-resistant weed distribution in Ontario. *Weed Technol.* 4:199-207.

Streber, W. R. and L. Willmitzer. 1989. Transgenic tobacco plants expressing a bacterial detoxifying enzyme are resistant to 2,4-D. *Bio/Technol.* 7:811-816.

Swanson, E. B., M. P. Coumans, G. L. Brown, J. D. Patel, and W. D. Beversdorf. 1988. The characterization of herbicide tolerant plants in *Brassica napus* L. after in vitro selection of microspores and protoplasts. *Plant Cell Reports* 7:83-87.

Swanson, E. B., M. J. Herrgesell, M. Arnoldo, D. W. Sippell, and R. S. C. Wong. 1989. Microspore mutagenesis and selection: Canola plants with field tolerance to the imidazolinones. *Theor. Appl. Genet.* 78:525-530.

Sweetser, P. B., G. S. Schow, and J. M. Hutchinson. 1982. Metabolism of chlorsulfuron by plants: Biological basis for selectivity of a new herbicide for cereals. *Pestic. Biochem. Physiol.* 17:18- 23.

Tauer, L. W. and J. Love. 1989. The potential economic impact of herbicide-resistant corn in the USA. *J. Product. Agric.* 2:202-207.

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