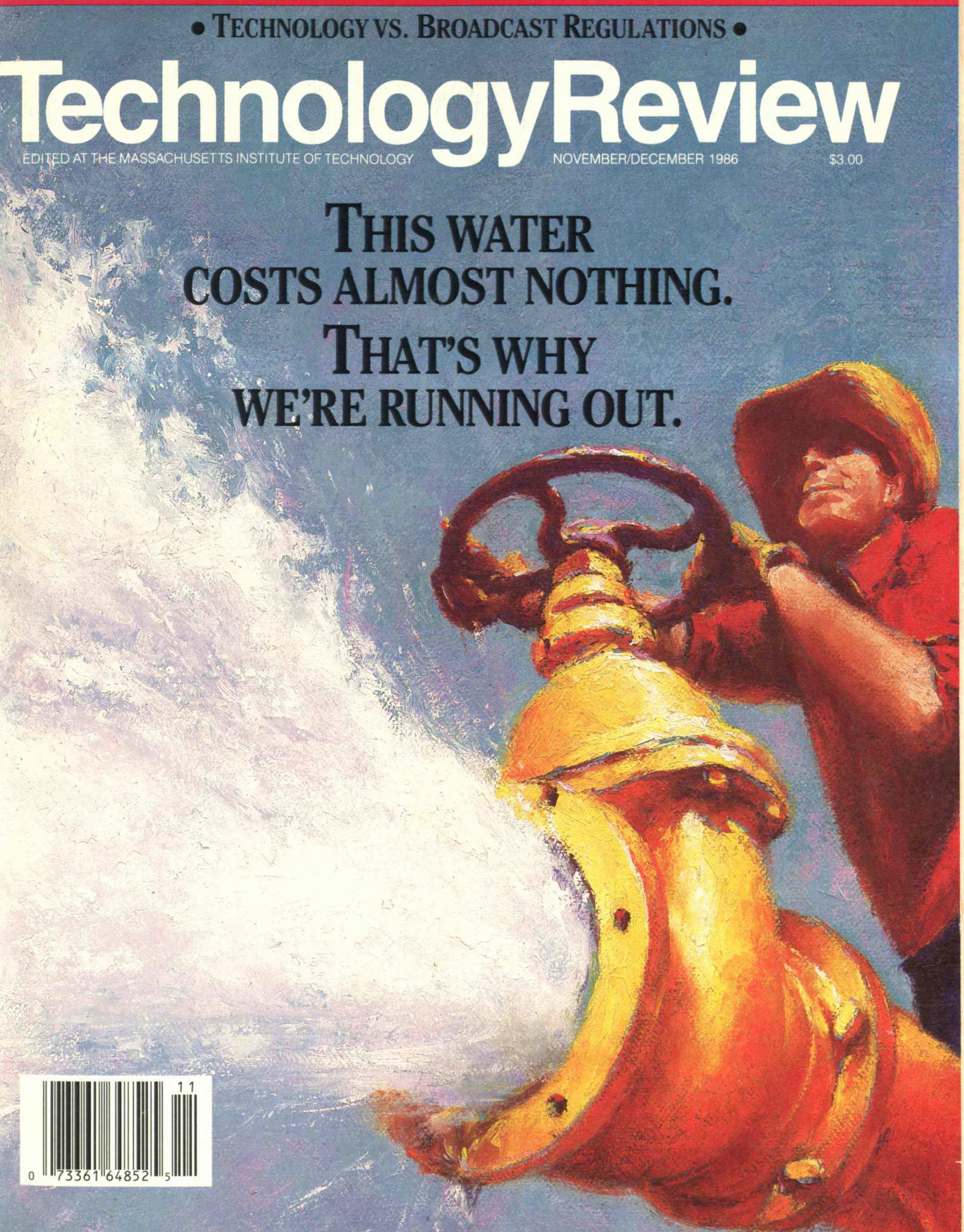
• THE MIDGETMAN DEBATE • WORKPLACE SURVEILLANCE •

• TECHNOLOGY VS. BROADCAST REGULATIONS •

TechnologyReview

EDITED AT THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY NOVEMBER/DECEMBER 1986 $3.00

THIS WATER COSTS ALMOST NOTHING. THAT'S WHY WE'RE RUNNING OUT.



NOV/DEC 1986 VOL. 89 NO. 8

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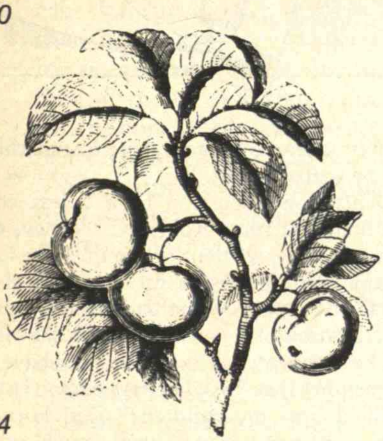
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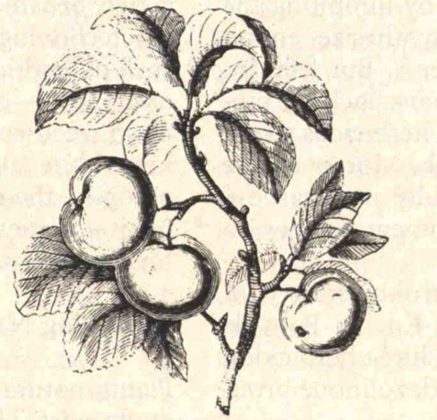
COVER
Illustration by Paul Mock
Design by Nancy Cahners

We can reduce our dependence on cancer-causing herbicides by breeding crops that resist more benign compounds.

Engineering Crops to Resist Herbicides



In the past 30 years, the use of chemical herbicides has become established agricultural practice in developed countries. Today more than 95 percent of the acreage devoted to most major field crops is treated with at least one and often two to five herbicides annually. Two or more products are generally needed to control grass and broadleaf weeds. In many cases one herbicide controls weeds that germinate in early spring, while others control later-sprouting weeds.

By eliminating weeds that compete with crops for nutrients and water, herbicides have helped farmers substantially raise their profitable yields. Plant breeders have produced varieties that can be cultivated much more densely. It is now common for farmers to plant 24,000 corn seeds per acre, in contrast to 14,000 before the advent of herbicides and synthetic fertilizers.

But herbicide use requires major cash outlays. For many field crops, farmers now spend about as much on herbicides as on seed. In this era of poor farming returns, every component of production costs is under continuous scrutiny.

The economics of weed control is not the only herbicide-related concern in farm country. Mounting evidence indicates that herbicides can cause serious public-health problems and environmental damage. In the last few years, toxicological studies have shown that many herbicides can cause cancer and other chronic diseases. Epidemiological studies have also linked certain herbicides with cancer. In addition, because farmers are so familiar with herbicides, they tend to be lax about following safety precautions on product labels. So occupational exposure is a growing concern.

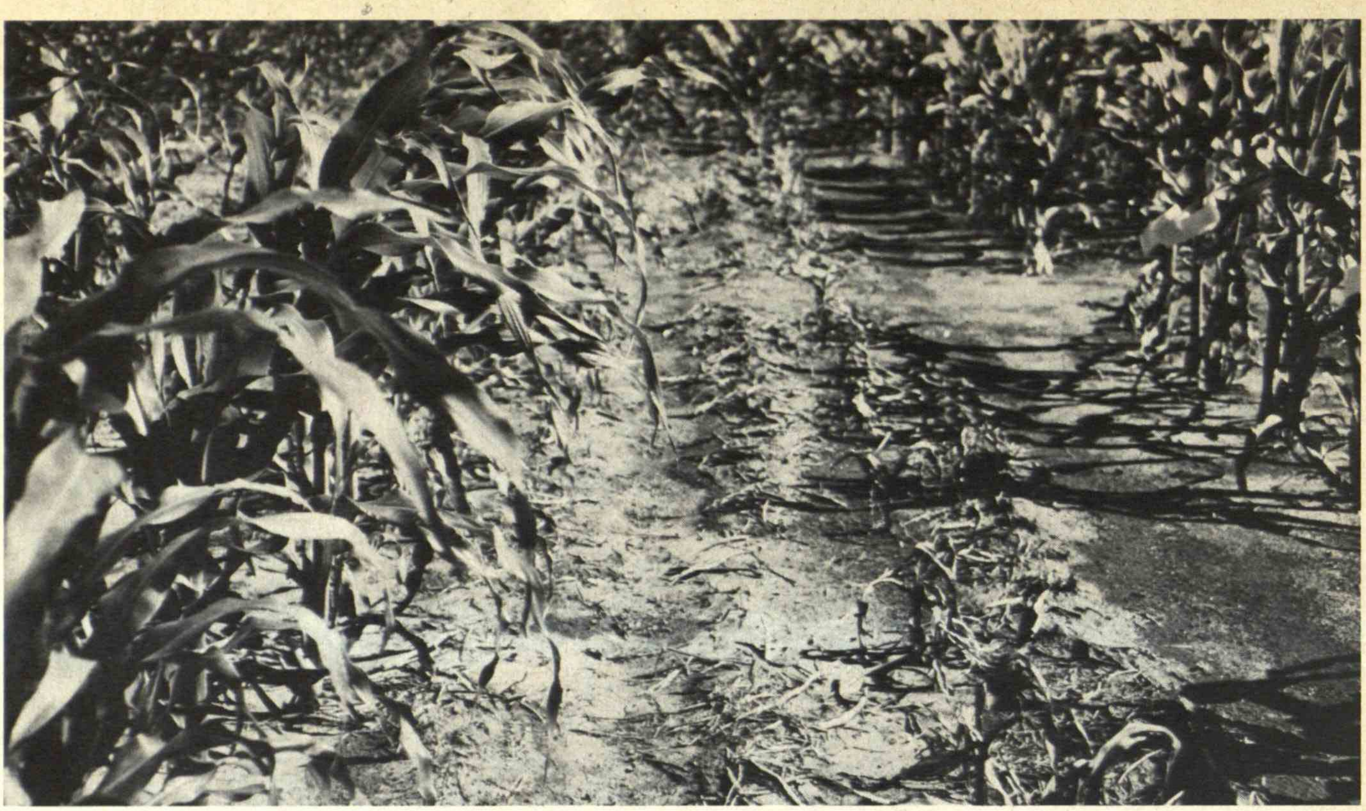
The recurrent detection of herbicides in surface-water and groundwater supplies creates broader public-health worries. Two of the most frequently detected contaminants—alachlor and atrazine—cause cancer in long-term animal tests. These herbicides are the most widely used in the United States. They are applied to about one in every three acres of cropland each year, primarily for controlling a wide variety of grassy weed species.

In the next few years, regulatory restrictions on certain herbicides could accelerate the rate at which newer and highly effective herbicides are adopted. At least six major herbicides were registered for crop use by the U.S. Environmental Protection Agency (EPA) in the first half of 1986. A comparable number are in the regulatory pipeline and likely to be available for the 1987 crop season.

BY CHARLES M. BENBROOK AND PHYLLIS B. MOSES

Left: Tobacco flowers are covered with paper bags to prevent haphazard pollination during conventional cross-breeding. This technique can be used to develop herbicide resistance in some plants.

PHOTO: JOHN COLWELL, GRANT HEILMAN PHOTOGRAPHY



Some new chemicals kill plants by inhibiting the action of certain enzymes that synthesize amino acids, the building blocks of proteins. But fish, insects, and mammals, including humans, lack the biochemical pathways upon which the herbicides work. So these species face little or no risk. Moreover, the herbicides either break down rapidly into carbon, nitrogen, and oxygen in the environment, or they do not leach appreciably into water.

The breakthroughs in weed-control chemistry include Monsanto Co.'s glyphosate, E.I. du Pont de Nemours & Co.'s family of sulfonylurea herbicides, and American Cyanamid Co.'s imidazolinone products.

These herbicides are highly effective and desirable from an environmental perspective. But their broad spectrum of activity is a roadblock to widespread use. Many of the chemicals discriminate poorly, if at all, between weeds and crops. They are not likely to be used to their full potential unless crops can be made to resist the toxic effects. This fact has fueled extensive private-sector research and development on herbicide-resistant crop varieties.

Seed, chemical, and biotechnology companies are starting to develop plant varieties that have natural or genetically engineered resistance to specific, highly active, broad-spectrum herbicides. These efforts and the technologies expected to evolve from them—such as herbicides designed for improved efficiency and safety—could begin to have profound effects upon weed-control practices and the herbicide market within 10 years. Of all emerging plant biotechnologies, the new herbicides and herbicide-resistant plant varieties probably offer the greatest potential for short-term gains in agricultural productivity.

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Exploiting Natural Resistance Traits

Plants naturally resistant to specific herbicides already exist. Their resistance stems from some special genetic trait. For example, wheat is naturally resistant to Glean, a sulfonylurea compound marketed by du Pont. Were it not for natural resistance, selective chemical herbicides for agricultural applications would not be possible: all herbicides would kill all plants.

Resistance traits usually take one of four forms. In one form, the plant does not absorb the herbicide. In another, the plant does not transport the herbicide into those tissues where it can do damage. Or the plant may detoxify the herbicide by breaking it down. Finally, the site within the plant's cells where the herbicide would act may not be susceptible. Sometimes the site is not susceptible because the herbicide cannot bind to the target protein, which may be an enzyme crucial for manufacturing a group of essential amino acids. In other cases, the herbicide can bind, but the target protein can still carry out its function.

Left: After an application of one type of imidazolinone, the left row of resistant corn grew, while the center row of non-resistant corn withered. Below: Lab tests show that the active ingredients of some broad-spectrum herbicides are less toxic than those of many other herbicides. More than twice as much glyphosate, imazaquin, or chlorimuron ethyl as alachlor or atrazine is needed to kill 50 percent of a group of rats. Crop lines are being developed to resist these broad-spectrum herbicides.

ACTIVE INGREDIENT	BRAND NAME	YEAR INTRODUCED	ACUTE TOXICITY (mg. of compound/kg. of body weight)	RATE OF APPLICATION (lbs./acre)
Broad-spectrum herbicides:				
Glyphosate	Roundup	1976	4,300	0.5
Imazaquin (an imidazolinone)	Scepter	1986	5,000	0.125
Chlorimuron ethyl (a sulfonylurea)	Classic	1986	4,100	0.03
Other herbicides:				
Alachlor	Lasso	1969	1,800	2.5
Atrazine	AAtrex	1967	1,780	1.8

Scientists can create resistant crops through conventional plant breeding, cell-culture techniques, and recombinant-DNA methods. Conventional plant breeding is the simplest route. It allows researchers to transfer naturally occurring resistance traits in crops or weeds to new species. For example, Canadian breeders have created resistant crops by crossing weeds resistant to the older, popular herbicide atrazine with rutabaga and rapeseed, an oil-producing plant. As a result, atrazine can be used on crops in northern latitudes, where field conditions render other forms of weed control ineffective.

The plant lines that resulted from conventional breeding of rutabaga and rapeseed had lower crop yields because the process interfered with photosynthetic responses. In general, however, scientists try to select crossed plant lines that do not differ from the parent crops except in resisting herbicides. They expect that such selection will be possible with the newer, broad-spectrum herbicides, although not many plant lines have been cultivated to resist them.

One difficulty with conventional plant breeding is that it can be done only with two closely related plant species. For example, to produce offspring, the plants' sex cells must have the same number and configuration of chromosomes, which carry the genetic information. Nature has evolved mechanisms, which are not completely understood, to make sure that very different plant species do not interbreed.

Cell-culture techniques, which may succeed when conventional breeding fails, can also halve the time needed to develop a resistant variety. The techniques involve growing whole cells in a petri dish. In one approach, a chemical is added to fuse a cell from a resistant plant with a similar cell from the susceptible crop. The parent plants must still be fairly closely related. Otherwise the fused, hybrid cell will not regenerate into an entire fertile plant. Once a fertile plant is regenerated, it must be backcrossed—bred for several generations with the crop parent, as in conventional breeding—to obtain herbicide-resistant plants that exhibit the original crop's desirable traits, including yield, nutritional quality, and disease resistance. This approach has been used successfully to transfer atrazine resistance into cultivated potatoes from *Solanum nigrum,* a related weedy species.

A second cell-culture method relies upon selecting those rare cells in a large laboratory culture that become resistant to the herbicide through mutations. These can occur spontaneously or with the help of mutagenic chemicals. Scientists induce the resistant cells to regenerate into whole plants by applying hormones. The regenerated plants are then tested for retention of the resistance trait. No backcrossing is needed if the cells come from the original desired crop variety. Several crops resistant to the new, broad-spectrum herbicides have been created through this cell-culture method. The successes include an alfalfa line that resists the compound glyphosate, corn that can withstand imidazolinones, and tobacco that can survive sulfonylurea herbicides.

Resistance through Recombination

Naturally occurring resistance traits and traits selected in cell cultures often stem from mutations in single genes. Genes, which carry traits encoded in DNA, can be manipulated by molecular biologists who isolate, further mutate, and recombine them in the test tube. The scientists then reintroduce the manipulated genes into plants.

Active research is focused on finding or creating resistance genes for a number of herbicides and transferring these genes into crops. Scientists must first understand the biochemical mechanism and metabolic target of an herbicide. Consider the development of several plant lines that resist glyphosate, one of the broad-spectrum herbicides. Detailed studies show that glyphosate kills plants and bacteria by binding to and inhibiting the action of an enzyme called EPSPS, which is needed to synthesize several amino acids. In 1983, scientists working at the bio-

PHOTO: ROB FINCHER, PIONEER HI-BRED INTERNATIONAL; CHART: RICHARD WILES, NATIONAL ACADEMY OF SCIENCES

California tomato growers could cut their weed-control costs by more than three-fourths by using herbicide-resistant plants.

technology company Calgene, Inc., in Davis, Calif., selected bacteria resistant to glyphosate's inhibitory effects. From these bacteria they obtained a gene encoding an EPSPS enzyme that resists glyphosate. They engineered this gene into tomato, tobacco, cotton, and poplar cells to grow plants that can tolerate glyphosate.

This strategy is feasible for many plant species. One variation is to select and engineer a resistance gene from plant cells rather than from bacteria. Another is to custom design a resistance gene in the test tube by chemically changing a non-resistant gene's DNA. This direct engineering is based upon chemical knowledge of the target protein's structure and its interaction with the herbicide.

Scientists have also found that they can overcome an herbicide's toxic effect by promoting surplus production of the target protein. To accomplish this, they splice certain regulatory signals into the plant's DNA. Monsanto scientists have used this technique to create tomato, tobacco, and petunia plants that resist glyphosate by producing 20 to 40 times more of the enzyme EPSPS. The scientists are striving to augment this resistance by directly engineering precise chemical mutations in the gene that would make EPSPS intrinsically resistant to glyphosate.

At the rate biochemical technology and techniques for genetic engineering are progressing, in about 10 years it will be as routine to create resistance genes via test-tube mutations as it is now to select such genes by contemporary cell-culture methods.

Corporate Payoff Potential

At least two dozen agrochemical and biotechnology companies are engaged in research to create crops resistant to chemical herbicides. The most extensive programs revolve around the three classes of broad-spectrum herbicides already mentioned: glyphosate and its related compounds, sulfonylureas, and imidazolinones.

The first and perhaps the only herbicide ever to reach $1 billion in annual sales—glyphosate, developed and marketed by Monsanto—indiscriminantly kills both crops and weeds. The remarkable commercial success of this product, which was introduced in 1976, stems largely from its broad array of uses, which offset the relatively high cost per pound of active ingredient: $22, in contrast with $4.50 for alachlor and $2.40 for atrazine. Today, glyphosate is used to control weeds in urban and industrial settings, to kill weeds, shrubs, and deciduous trees in forests, and to destroy aquatic vegetation. Because of its high cost, farmers use it sparingly for weed control before planting crops in reduced or no-till farming systems, and for range, orchard, and other specialty-crop situations in which the herbicide can be placed just where needed.

A decade ago Monsanto recognized the tremendous payoff to be realized by engineering glyphosate resistance into major crops. If resistant alfalfa, soybean, and corn varieties could be engineered, the prospective annual U.S. market for glyphosate would expand from a few million acres of cropland to nearly 150 million. To penetrate that market, the cost of glyphosate would have to fall somewhat. But if it did, the herbicide's profit potential could rise 10 times or more.

Even at today's prices, glyphosate would be cost-effective for certain farmers. For example, if a suitable tomato line were available, California tomato growers could spend just $30 per acre for weed-control costs, down from their current $130 per acre. The savings would result from eliminating both supplementary hand weeding and a combination of expensive herbicides that are only partly effective.

Glyphosate is not the only compound for which companies are developing resistant crop lines. Biotechnologists at du Pont, which developed sulfonylurea herbicides, have selected tobacco cells that resist sulfonylureas because of a minor change in the chemical structure of the target protein. Work is underway to transfer the resistance gene into corn, soybeans, and alfalfa.

At American Cyanamid, which created imidazolinone herbicides, scientists have regenerated imidazolinone-resistant corn plants from cultures of resistant corn cells. In a collaborative project with the seed company Pioneer Hi-Bred International, the resistance gene is being bred into Pioneer's corn lines. Researchers expect that careful backcrossing of resistant varieties with inbred corn lines will produce superior resistant hybrid lines ready for marketing by the early 1990s.

In our view, the companies' prospects for sales increases are modest compared with the total volume of business conducted by them. Only a limited number of farmers would likely switch to American Cyanamid's herbicide and Pioneer's seed corn at imidazolinones' current prices of about $120 per

pound of active ingredient. Farmers have other well-proven, effective products available. However, many might switch if imidazolinones could be sold for perhaps $50 per pound—and if the performance of the new resistant hybrids proves comparable to that of other varieties.

But how well the newer products would sell would also depend on the possible competition from both new and old products. Moreover, farmers tend to be skeptical about new technologies. Many prefer to see how successfully they are used by others. In addition, the biotechnologies used in developing one resistant crop variety are likely to be applied with equal success to other varieties. Hence, crop varieties resistant to particular herbicides may be unique for just one or a few seasons. We do not expect that any single herbicide or crop variety will be able to offer sufficiently compelling advantages to set in motion major shifts in herbicide and seed selection.

For this reason, it is not likely that the structure of agribusiness will change dramatically simply because of herbicide-resistant plants. Critics fear that recent mergers of chemical and seed companies will enable some firms to gain a greater share of the herbicide market if they package the new compounds with herbicide-resistant plants. And presumably, farmers would be lured into paying more for such products. But many chemical companies that moved quickly into the seed industry are regretting their haste because the short-term profits that they once hoped for do not seem realistic anymore.

It seems to us that when the private sector finances research in herbicide resistance, the purpose is just as much to explore a valuable technological frontier as to reap short-term commercial gains. Research will lead to a better understanding of basic plant biology, and scientists will learn how to introduce other characteristics, such as disease resistance, into plants. Already scientists at Washington University, in collaboration with Monsanto, have genetically engineered tomato and tobacco plants to resist a viral disease that causes significant losses to farmers. Resistance research is also providing critical insights into how herbicides work. In the past, finding herbicides involved testing tens of thousands of compounds for their ability to kill weeds. In the future, herbicides may be designed to exploit a given plant's biochemistry.

PHOTO: JOHN COLWELL, GRANT HEILMAN

Government Approvals Expected

The company with herbicide-resistant plant lines closest to federal review is Calgene. Its glyphosate-resistant tomato, tobacco, and poplar lines are ready for field trials pending the requisite government approvals, which are expected. Despite considerable controversy about federal regulations for genetically engineered products, there is little indication that herbicide-resistant crops will face a challenge in the regulatory arena. No unique environmental or ecological concerns have been associated with resistant cultivated plant lines, regardless of fears about genetic engineering.

Arguments claiming that herbicide-resistant crops may pose ecological dangers do not hold up. One such argument is based on the notion that resistance traits could spread from crop plants to weeds. However, the 40-year history of synthetic-herbicide use provides surprisingly few examples of transfer of herbicide-resistance genes to and among weed species. There is no reason to expect the incidence to rise with genetically engineered resistant crops. Moreover, herbicide resistance in a weed species merely compels a change in farm management. Farmers have dozens of choices: mechanical cultivation, new herbicides, crop rotations, and so on.

A second concern that has been raised stems from the notion that a crop genetically engineered to resist an herbicide will somehow be physiologically weaker than the original variety or more susceptible to mutations. But it is very unlikely that flaws in a new variety could go unnoticed, given the sophistication of contemporary plant breeding. And even if weaker varieties did develop from plant breeding, they would not be commercialized. Seed companies thoroughly test new crop varieties.

Another argument sometimes raised against herbicide-resistance technology is that it will accelerate the world's dependence on a few crops and a narrow genetic base. History amply demonstrates that huge areas planted with a single crop variety can be devastated by a new disease or environmental problem to which that variety is not resistant. Yet there is little chance that herbicide-resistant varieties will substantially alter the genetic base of crop plants. Nor are they likely to have a significant effect on land-use patterns, which have already progressed a

Far left: The herbicide alachlor is poured into a container. Some herbicides would be better packaged in containers that dissolve in water. Farmworkers would avoid exposure during mixing. Left: An herbicide is loaded onto a spray plane.

long way toward monoculture in many regions of the world. Indeed, resistant varieties could actually decrease monoculture in some areas by allowing farmers to plant new crops and follow new rotations where weed-control problems had previously prevented changes.

Rather than posing unprecedented or unique environmental concerns, the new herbicides protect public health. They have not proven to be toxic to animals, including humans. And before gaining EPA registrations, they have had to withstand a much more complete battery of ecological and toxicity tests than most of the older herbicides. During the 1970s, the EPA toughened the rules for testing pesticides, largely in response to the environmental movement.

Tighter Regulation of Existing Herbicides

The tighter regulations are also requiring the retesting of the older herbicides. New chronic-toxicity data have become available on several older herbicides, including atrazine and alachlor, which account for 36 percent of all herbicide use in this country. In June 1986 the EPA received data indicating that atrazine increased the probability of malignant mammary tumors in rats. Data on alachlor submitted to the agency in 1983 raised even more serious concerns. This herbicide triggered several types of tumors in different animals.

The information has raised new fears about the long-term consequences of farmers' exposure to herbicides. In addition, EPA and state officials have been evaluating the significance of exposure to these chemicals in drinking water. Alachlor and atrazine are found routinely in surface water in U.S. agricultural areas and migrate into aquifers.

Public-health risk from alachlor in drinking water is causing the EPA the most difficulty. Questions have surfaced regarding what level of cancer risk is acceptable for a local population facing a high risk or a distant, larger population facing a more uncertain risk. By early this fall, the EPA had banned the use of alachlor on certain crops, including potatoes, and was deliberating whether to restrict or ban its use entirely.

New regulations on several other carcinogenic
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PHOTOS: GRANT HEILMAN; ALAN PITCAIRN

HERBICIDES

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herbicides may also be imposed in the next two to four years. The EPA will no doubt need more data before decisions can be made. It is particularly important that the EPA's long-awaited groundwater-monitoring survey—which is expected to end in 1987—be completed with dispatch and great attention to detail.

Many older herbicides pose some carcinogenic risks. It appears that none is a potent carcinogen like the pesticide ethylene dibromide (EDB), which has now been banned, but it is very hard to estimate how great the human cancer risks are. Because of the wide use of carcinogenic herbicides, the EPA should find more compelling ways to convince farmers to comply with the safety precautions on herbicide labels. Herbicide spraying systems should also be changed to better protect agricultural workers, as should the packages and formulations in which the herbicides are sold. For example, the EPA could require that concentrated herbicides be packaged in containers that dissolve in water, so farmers don't run the risk of touching the chemicals. Or since farmers often apply two or more herbicides, the EPA could encourage the mixing of compounds at manufacturing plants.

And as they reassess these products, regulatory agencies should remember that many substitutes are available, and should consider the availability of new products.

Regulatory agencies may eventually recognize the size of the environmental gains from using the newer herbicides. The newer herbicides are generally applied at one-half to one-tenth the rates of the older products. Despite rigorous testing, they have not demonstrated mammalian toxicity, and they have little or no potential for migrating into groundwater. Also, they almost certainly will not raise farmers' production costs.

It is heartening that about three-quarters of the corporate R&D in herbicide resistance is targeted toward the newer compounds. The environment would benefit if research succeeds in broadening the uses of the highly active, newer herbicides. The question remains whether regulators and corporate financiers will have the vision to fully exploit this potential. □

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