A Growing Threat Down on the Farm

Farmers have become dependent on a herbicide called glyphosate and on crops engineered to resist it. Now, weeds are becoming resistant, and researchers are scrambling for alternatives.

Conventional wisdom has it that biotech drugs have flourished while genetically modified (GM) crops have foundered because of protests in Europe and elsewhere. Not so. Biotech drugs are doing just fine and, it turns out, so are GM crops. Last year, 10 million farmers in 22 countries planted more than 100 million hectares with GM crops. Over the past 11 years, biotech crop area has increased more than 60-fold, making GM crops one of the most quickly adopted farming technologies in modern history (see figure, p. 1115). Even the European Union is beginning to embrace them, with six E.U. countries now planting GM crops.

What’s behind this blossoming of transgenics? Oddly enough, a herbicide called glyphosate. The compound is the world’s best-selling herbicide by far, prized by farmers for its safety and effectiveness at wiping out hundreds of different kinds of weeds. That effectiveness has not only convinced farmers to make the switch but also prompted seed companies to engineer crops to be impervious to glyphosate’s effects. That has allowed farmers to spray their growing crops to wipe out encroaching weeds without fear of wiping out their livelihood. The model has proven so successful that of the transgenic crops planted worldwide last year, approximately 80% were engineered to be glyphosate-resistant (GR).

“The rate at which this technology has been adopted floors me,” says Donald Weeks, a plant biochemist at the University of Nebraska, Lincoln.

But this success has sown the seeds of its own potential demise. Much of modern agriculture is now dependent on a single chemical. “Glyphosate is as important to world agriculture as penicillin is to human health,” says Stephen Powles, who directs the Western Australian Herbicide Resistance Initiative in Perth. It’s an apt comparison, because just as pathogens have grown resistant to penicillin and other antibiotics, weeds resistant to glyphosate have recently begun sprouting and spreading around the globe. For now, the scale of the outbreak remains small. But agricultural experts worry that herbicide-resistant weeds are...
posed for their own takeover. “There is going to be an epidemic of glyphosate-resistant weeds,” Powles says. “In 3 to 4 years, it will be a major problem.” If farmers and seed companies lose their ability to rely on glyphosate, it could cost them billions of dollars in lost productivity. But the damage will likely be more than monetary, as it could also have a major environmental consequence as well (see sidebar, p. 1116).

In the face of this threat, agricultural researchers are mounting a multifaceted campaign to safeguard glyphosate and come up with other options in case its effectiveness wanes. On page 1185, for example, Weeks and his colleagues at Nebraska report that they have developed the first transgenic crops resistant to an alternative herbicide called dicamba. Down the road, growers may soon switch transgenic crops much as doctors select antibiotics to stay one step ahead of pathogens. But for now, the fight is on to save glyphosate.

**Fantasy league**
The love affair between farmers and glyphosate was kindled long before biotech crops hit the fields. In 1970, John Franz, a chemist at Monsanto, discovered that the compound acted as a broad-spectrum herbicide, capable of killing an enormous variety of plants when deposited on the leaves of young seedlings. Later, researchers found that glyphosate wrecks its havoc by inhibiting an essential plant enzyme known as 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS). The enzyme catalyzes an intermediate step in the construction of a trio of aromatic amino acids, which in turn are vital for the production of key plant metabolites. Without EPSPS, the plants are starved of these metabolites and quickly wither and die.

Just as enticing was what glyphosate does not do. Although concerns have been raised about the surfactants that are used alongside glyphosate in most formulations, glyphosate itself does not appear to affect animals and insects, which don’t have EPSPS and rely on their diet for the amino acids the enzyme helps produce. And when sprayed on fields, glyphosate doesn’t readily leach into water systems. Instead, it latches tightly to soil particles and degrades within weeks into harmless byproducts. By contrast, herbicides such as atrazine have been widely implicated in contaminating groundwater.

Monsanto began selling glyphosate in 1974 under the trade name Roundup. Sales remained modest for years—until researchers engineered GR crops to use in combination with the herbicide. By 1983, researchers had isolated a gene known as CP4 in bacteria that synthesized aromatic amino acids through a different route from that of the EPSPS in plants. By 1986, they had spliced CP4 into plants and shown that the plants could withstand the effects of glyphosate with no apparent damage.

It was another 10 years before Roundup Ready soybeans hit the market, but their impact was dramatic. In 1995, U.S. farmers used 4.5 million kilograms of glyphosate; they now use 10 times that amount. “If I were playing in an herbicide fantasy league, my first pick would be Roundup Ready cropping systems with glyphosate, and I would let you have the next three selections,” says John Wilcut, a crop scientist at North Carolina State University (NCSU) in Raleigh.

Since 1996, Monsanto and other seed companies have introduced GR canola, cotton, corn, sugar beets, and alfalfa. The popularity of the herbicide was further fueled when the compound went off patent in 2000, which triggered a 40% price drop in the years since. That combination produced a massive shift from traditional crop varieties to GR versions. In just a 5-year span, GR soybeans commanded 50% of the land cultivated for soy in the United States, and GR corn a 40% share. Today, GR soybeans make up more than 90% of soybeans planted in the United States, and corn more than 60%. By comparison, organic agriculture accounts for about 1% of cultivated land. “Farmers are normally very conservative,” says Weeks. “Clearly, this was a real winner.”

**Awaiting the inevitable**
One effect of that winning combination has been to slash the market for competing herbicides. According to data from the U.S. Department of Agriculture (USDA), the prices of two popular herbicides—chlorimuron and trifluralin—have dropped 20% to 40% since 1998. Over the same period, U.S. sales of all herbicides, including glyphosate, have declined by about $1 billion, nearly 20% of the industry total. Faced with this shrinking market and the glyphosate juggernaut, herbicide companies have been backing out of the market. Nearly 20 herbicides with different mechanisms of killing plants were sprayed on soybeans a decade ago; now, farmers are increasingly relying on glyphosate for most or all of their herbicide needs. In a survey of 400 farmers in the U.S. Midwest, for example, researchers at Syngenta found that 56% of soybean growers in northern states and 42% in southern states use glyphosate as their sole herbicide. As a result, “the selective pressure for weeds to develop resistance has been huge,” says Stephen Duke, a plant physiologist at USDA’s Agricultural Research Service in Oxford, Mississippi. “From a biological perspective, this is inevitable,” adds Jerry Green, a weed scientist with DuPont Crop Protection in Newark, Delaware.

For years, many researchers doubted that plants would be able to overcome their vulnerability to glyphosate, because EPSPS plays such a vital role in plant metabolism. One 1997 paper in the journal *Weed Technology* even stated that “the complex mutations required for the development of glyphosate-resistant crops are unlikely to be duplicated in nature to evolve glyphosate-resistant weeds.” Unfortunately, that was written just after the first GR weeds were discovered in 1996. Today, about a dozen different varieties of weeds are known to have developed resistance. And the spread of resistance to new weed species is increasing. Resistant weeds have now been spotted in countries around the globe, including the United States, Argentina, South Africa, Israel, and Australia. According to WeedScience.com, an international herbicide-resistance tracking service, GR “horseweed” was first identified in a Delaware field of GR soybeans in 2000, and since then it has turned up in 14 states as well as in Brazil and China.

Again, like many microbes that evolve to outwit antibiotics, it now appears that
Weeds resistant to the powerhouse herbicide glyphosate not only threaten the livelihoods of farmers worldwide, but they could have environmental downsides as well. Among the worst, glyphosate’s disappearance could increase the loss of topsoil, require farmers to switch to more harmful herbicides, and force them to use more fuel to rid their fields of weeds.

The current combination of herbicide-resistant crops and herbicide use is hardly an environmental panacea. A 2003 farm-scale evaluation in the United Kingdom, for example, found that the combination contributed to a loss of biodiversity both by reducing the numbers of weeds and by indirectly affecting insects that rely on those weeds for food. Many governments have also been cautious about allowing the use of herbicide-resistant crops for fear that genes that confer herbicide resistance could spread far beyond agricultural fields.

Despite such concerns, many agricultural researchers now say glyphosate-resistant (GR) crops have had widespread environmental benefits, at least compared with the previously used alternatives. “Glyphosate-resistant crop weed management systems are generally safer to the environment than what they replace, and in many cases much safer,” says Stephen Duke, a plant physiologist at the U.S. Department of Agriculture’s Agricultural Research Service in Oxford, Mississippi.

One of the biggest benefits of GR crops is their indirect impact on topsoil. Modern farming encourages heavy topsoil losses because farmers traditionally plow fields before planting seeds. Turning over the topsoil buries many weed seeds that were present under 4 to 6 inches of dirt. Although that reduces the likelihood that weeds will compete with emerging crop plants, it also dramatically increases the amount of topsoil that washes away with rain and irrigation.

By contrast, many farmers don’t plow their fields before planting GR crops. Instead, they simply plant seeds and spray glyphosate on their fields shortly after their crops have emerged, wiping out their weedy competitors. The upshot is that herbicide-resistant crops often require minimal

GR weeds don’t make a frontal attack on glyphosate. According to Christopher Preston, a weed-management scientist at the University of Adelaide in Australia, one common resistance mechanism centers on the way glyphosate moves within plants. In a presentation at a symposium on glyphosate resistance held as part of the American Chemical Society (ACS) meeting in March in Chicago, Illinois, Preston noted that when glyphosate is sprayed on the leaves of a susceptible plant, it is normally absorbed quickly and moves readily throughout its tissues. Once inside, it accumulates at the growth point in roots and stems and kills the plants. However, when Preston and his colleagues looked at a resistant form of rigid ryegrass, they found that the glyphosate accumulated in the leaf tips. The plant was essentially steering the compound away from areas where it could inflict lethal damage. Preston’s team found a familiar mechanism of resistance in two populations of horseweed as well, suggesting that glyphosate sequestering could be a mode of resistance common to many weeds.

For now, however, resistant weeds are still the minority. According to the Syngenta survey, 24% of farmers in the northern portion of the Midwestern United States and 29% in the south say they have GR weeds. But only 8% say it’s a problem across all of their acreage. Still, Syngenta’s Chuck Foresman, who presented the data at the ACS meeting, says, “the resistance issue is across the Midwest, South, and Southeast. Nobody is exempt.” Crop scientists from Argentina, Brazil, and Australia echoed growing concerns about the problem in their countries as well.

What to do?

Fighting resistance is something of an uphill battle, says Duke. At the moment, not all farmers see resistance as a major issue, but by the time they do, resistance may be so widespread that it will be hard to combat. In recent decades, when resistance to one herbicide has spread, farmers have simply switched to another. But glyphosate’s recent dominance of the herbicide market has reduced work on alternatives just when they are needed most. “Weed control is shifting to herbicide-resistant crops, and so are the research budgets,” Green says. That’s bad news, NCSU’s Wilcut says: “We need to have more of a diversity of herbicides out there.” But there are no new silver-bullet herbicides that are safe and broadly effective waiting in the wings. “We are not likely to get additional herbicide modes of action,” Wilcut says.

With a multibillion-dollar market for herbicides and transgenic seeds at risk, agricultural researchers underscore the need to educate farmers to use long-standard methods of combating weeds, to preserve glyphosate’s effectiveness as long as possible. Among these, says Weeks, are traditional resistance-management strategies of rotating crops and using a variety of different herbicides to combat weeds, practices that hinder resistant organisms from gaining a foothold in their fields. In many cases, that’s likely to mean rotating in crops that don’t rely on using glyphosate.

Aside from proper stewardship practices, most researchers feel that the best hope for combating herbicide-resistant weeds is the continued development of transgenic crops. Nicholas Duck and colleagues at Athenix, a crop sciences start-up in Durham, North Carolina, for example, are developing crop varieties that are resistant to even higher levels of glyphosate. Planting them may allow farmers to buy some time by applying heavier doses of the herbicide to their crops, but it could add to the selective pressure on weeds to develop resistance.

Other companies, meanwhile, are pushing crops resistant to herbicides other than glyphosate. Bayer Crop Sciences, for example, has already commercialized soybean and corn seeds resistant to glufosinate, a herbicide that kills plants by a different mechanism from glyphosate’s. These crops, sold under the trade
The electron shi...ing enzyme plastids. The move offers two benefits, Weeks explains. First, the resistance-conferring enzyme works better because it can swipe the electrons it needs from the steady stream generated during photosynthesis. Also, like mitochondrial DNA, chloroplast DNA is inherited through the maternal side. That means a GM crop can’t spread resistance through wind- or insect-carried pollen, which comes from the male side.

Weeks says Monsanto has licensed the technology and that it could be commercially available within 3 to 4 years. If so, he says, it could allow growers to rotate their crops between varieties resistant to two different herbicides. “It gives farmers an alternative to the continual use of glyphosate-resistant crops,” Weeks says. And the development of herbicide-resistant crops won’t stop with dicamba. “We have the technology today to develop herbicide resistance to about anything we want to,” Green says.

Another approach being pursued at Monsanto and elsewhere is to combine, or “stack,” genes for resistance to multiple herbicides in the same plants. Researchers at Pioneer HiBred, a division of DuPont, for example, are working to create crops that are resistant to both glyphosate and herbicides that target a plant enzyme called acetyl-CoA synthase. ALS inhibitors have also been on the market for years and face resistant weeds of their own. And scientists elsewhere announced last year that they plan to create crops resistant to herbicides that inhibit ACCase, an initial enzymatic step in lipid synthesis that is critical to grasses. In addition to stacking traits for resistance to multiple herbicides, researchers at Pioneer and elsewhere are looking to add other traits to crops, such as heat and drought resistance, increased yield, and insect resistance. In some cases, they hope to add genes for novel nutrients and even pharmaceutical compounds. “There is a tremendous opportunity to do this for the next generation of traits,” Duck says. Although such efforts are still in the early stages, he adds, “in the future, everything is going toward product stacks.” The question is whether crops resistant to multiple herbicides will prolong the life of one of the farming community’s favorite herbicides.

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