Insect-resistant Bt GMO crops have helped cut pesticide use. Now Nature is pushing back

In 2006, a small airplane started buzzing each cotton field in Arizona, a thin, dust-like cloud trailing behind it. The dust was millions of insects called pink bollworms, and the flights were part of an audacious scheme to kill them off.

Pink bollworms are insidious foes of cotton. Their larvae burrow into the plant's seed pods, called bolls, destroying the fluffy fiber within. Where bollworms infest a field, farmers may spray insecticides many times a year to limit the damage. But the air-dropped insects released in Arizona had been exposed to radiation that left them sterile, so any pink bollworms on the ground that mated with them would produce no larvae.

As part of an effort to eradicate the pink bollworm (Pectinophora gossypiella) from cotton-growing regions in the US, scientists bred the insects (shown) and briefly irradiated the adults, rendering them sterile. Billions of sterile pink bollworms were then released from airplanes over cotton fields, overwhelming wild populations with mates that couldn't produce offspring. Credit: Alexander Yelich via University of Arizona

The sterile insects were only the mopping-up part of an eradication campaign. The cotton plants themselves had struck the first, most vital blow. Genetically modified with genes obtained from an insect-killing bacterium called *Bacillus thuringiensis*, or Bt, the plants churned out proteins that are toxic to pink bollworms, making cotton bolls a deadly meal for the larvae.

By 2013, pink bollworms had vanished from Arizona's cotton fields. In 2018, the US Department of Agriculture declared that the pest had been eradicated from the United States.

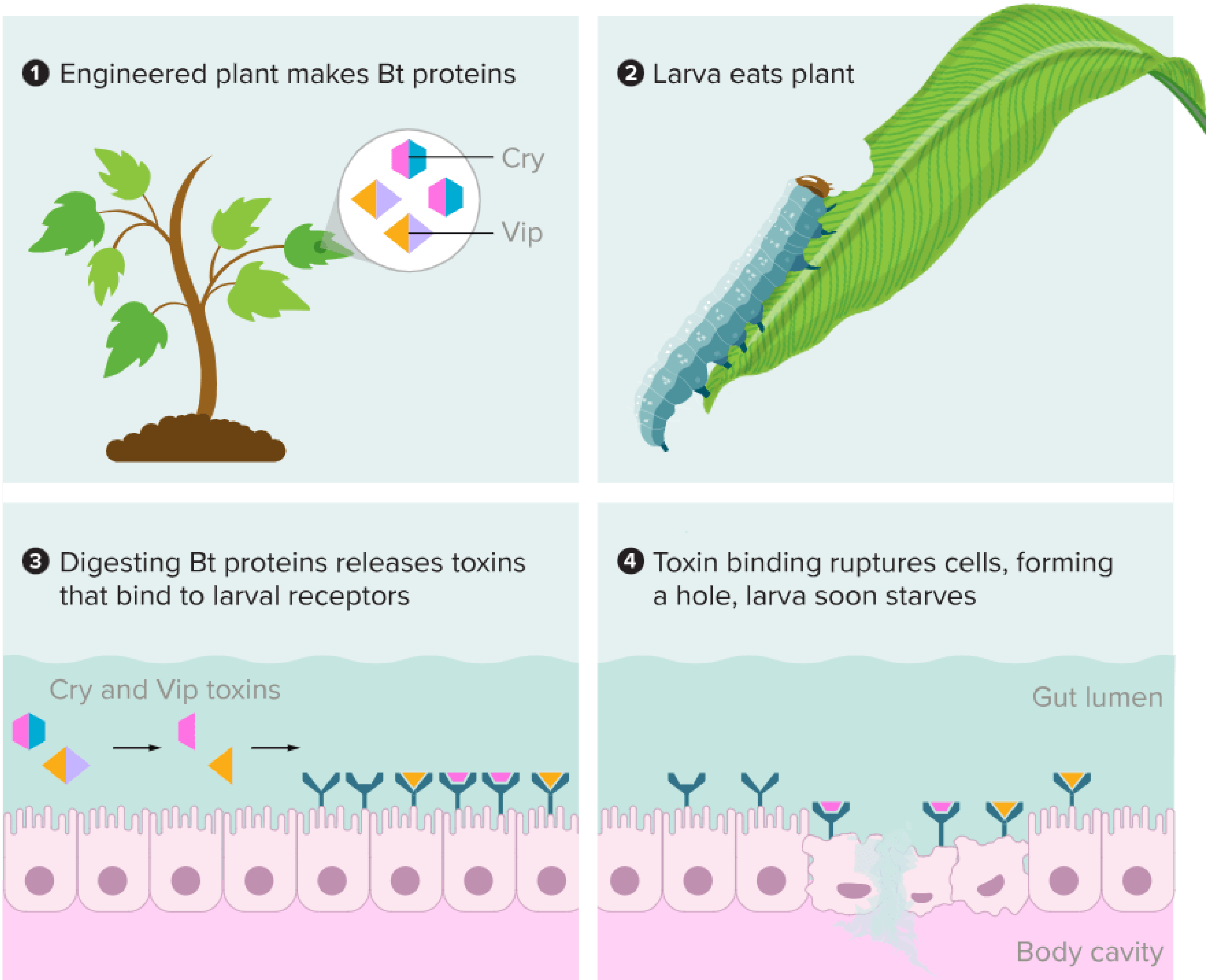
It was a remarkable success. Yet the story of engineered Bt cotton and corn also includes repeated failures. In the decades since the crops went on sale in 1996, other insects, such as the corn rootworm and the cotton bollworm (a different species from the pink bollworm), have evolved resistance to not just one but a whole series of toxins from *B. thuringiensis*. Today, there's just one remaining Bt gene, called *Vip3A*, whose toxins reliably kill two pests of corn and cotton, the western bean cutworm and the cotton bollworm. And there are signs that this vital tool, especially for cotton farmers in the southeastern United States, may soon become ineffective.

In an effort to keep these toxins working against the cotton bollworm, a group of academic entomologists has called on the US Environmental Protection Agency to sharply restrict their use, blocking the sale of corn containing the *Vip3A* gene throughout the South. That way, fewer insects will be exposed to its toxins, lowering the chances that a resistant strain will emerge. Companies that sell Bt corn, including Bayer and Syngenta, oppose this step. EPA officials hope to issue new rules for managing *Vip3A* and other Bt genes later this year.

It's just the latest round of a conflict that has accompanied these crops since before they were launched, one that pits the urge to profit from them against the desire to preserve their effectiveness. Scientists have typically advised restraint; they believed, based on theoretical models of insect evolution, that overusing these tools might quickly render them ineffective against many insects. To a remarkable degree, they were correct. Their models foresaw both the successes and the failures of Bt crops, and described ways to prevent, or at least delay, the emergence of resistant insects. But those recommendations often included drastic limits on Bt crop use, which companies successfully resisted.

Some scientists are disturbed to see the caterpillar-killing toxins from *B. thuringiensis* so quickly squandered. "Seeing resistance now to these traits can be quite disheartening, because there's so much promise" for reducing insecticide use, says Julie Peterson, an entomologist at the University of Nebraska—Lincoln.

How Bt plants kill insect pests



SOURCE: ADAPTED FROM M. NIEDERHUBER / *INSECTICIDAL PLANTS: THE TECH AND SAFETY OF GM BT CROPS* 2015 KNOWABLE MAGAZINE

Bt crops will kill only insects that have specific receptors in their gut; some Bt proteins are toxic to caterpillars, others to mosquitoes, still others to root worms. Plants are genetically engineered to produce specific Bt proteins, such as Cry and Vip proteins, in their tissues. When an insect eats the leaves, the Bt proteins begin to break down in its gut. This releases the toxic portion of the proteins. If cells in the insect gut have receptors for the toxins, those toxins bind to the receptors, the cells rupture and the insect starves.

A remedy for resistance

Bruce Tabashnik, an entomologist at the University of Arizona, encountered the ecological theory that shaped the fate of Bt crops in the early 1980s, long before those crops even existed. He refused to accept it at first.

He was a postdoctoral researcher at Michigan State University, intrigued by mathematical models that predicted how insect populations become resistant to insecticides. The models showed something that he didn't expect: Insects exposed to extremely high doses of insecticide evolved resistance more slowly than those given more modest doses.

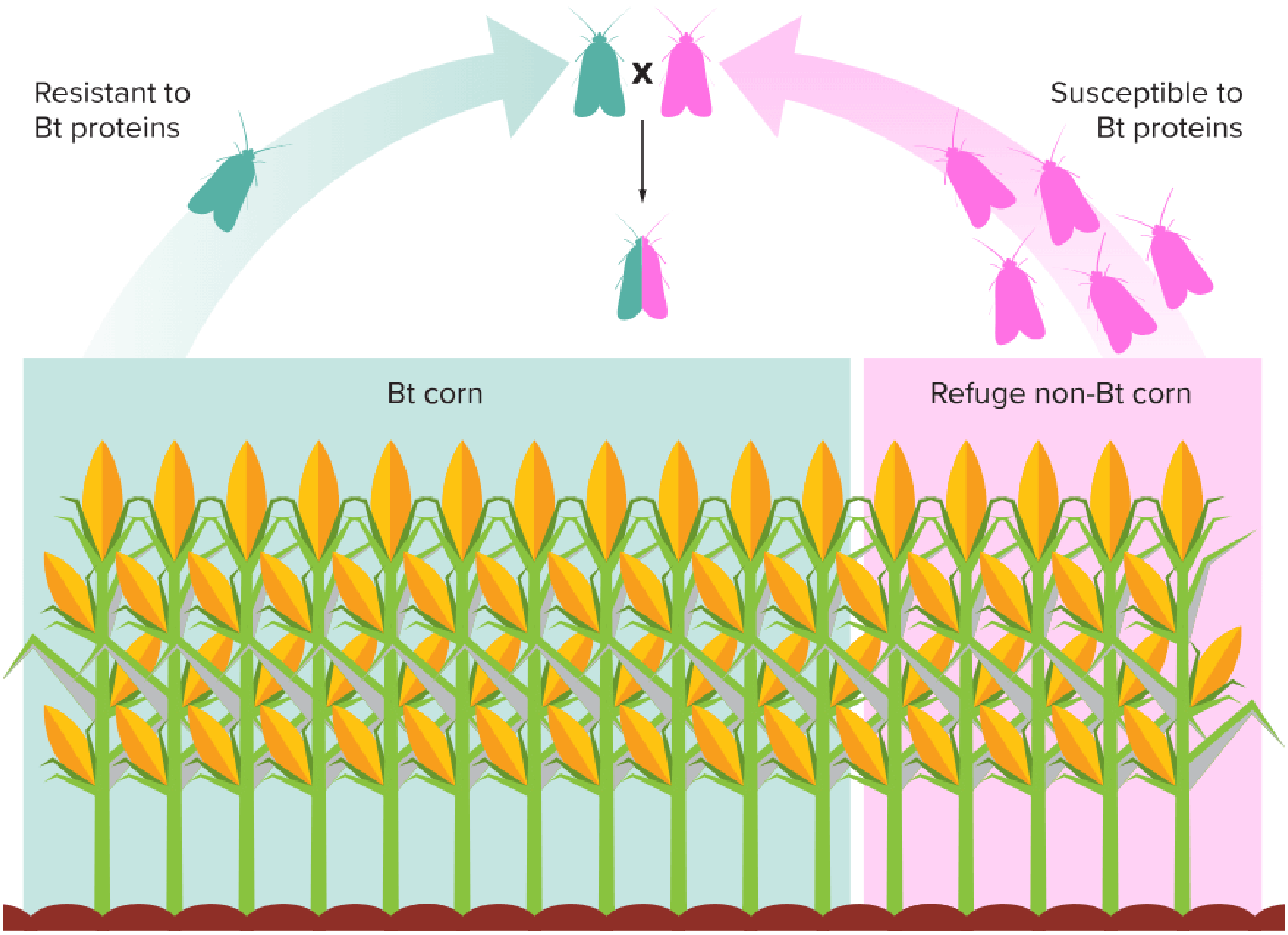
"I didn't believe it," Tabashnik recalls. "I thought that the higher the dose, the higher the concentration of insecticide — that resistance would evolve faster. It just makes more sense to me." He built his own model to check the calculations and got the same result. "I kept doing it over and over and over," he says.

Tabashnik finally realized that the models factored in something key: Insects could migrate. If a field was sprayed with insecticide, wiping out most insects, it might quickly be repopulated with insects from elsewhere that had never been exposed to the chemical. This had a profound effect. The rare insects that survived a powerful dose of chemicals, perhaps because of their genetic makeup, were likely to mate with one of the insects that flew in from elsewhere instead of another resistant insect.

The model revealed a novel two-pronged strategy for keeping insects susceptible to insecticides: first, a powerful dose of insecticide, and second, a "refuge" nearby where insects wouldn't be exposed. This haven would act as breeding ground for insects that remained susceptible, and their presence would lower the odds that survivors of spraying would mate with each other and produce resistant offspring. "That's really the major discovery of this whole theoretical field," Tabashnik says.

The high-dose/refuge strategy, as it became known, was merely a theoretical possibility at the time. "The idea just kind of sat there," says Aaron Gassmann, an entomologist at Iowa State University.

The high-dose and refuge strategy



SOURCE: ADAPTED FROM S.E. NARANJO *ET AL / THE ROLE AND USE OF GENETICALLY ENGINEERED INSECT-RESISTANT CROPS IN INTEGRATED PEST MANAGEMENT SYSTEMS* 2019

KNOWABLE MAGAZINE

The high-dose/refuge strategy can delay the evolution of insects that are highly resistant to Bt proteins. It works like this: Part of a field is planted with a Bt crop, such as corn, that delivers a high dose of toxin to a specific pest. A portion of that field, the refuge, is planted with a non-Bt version of the same crop. Few individuals should develop resistance to the Bt toxins, but if they do, they are more likely to mate with a susceptible individual than a resistant one. If the susceptible trait is dominant, any resulting offspring should be susceptible too.

Then, in the 1990s, the company Monsanto published data showing that its experimental corn and cotton containing genes from *B. thuringiensis* were incredibly lethal to many larvae from the Lepidoptera insect family. When the larvae fed on these plants, they ingested Bt toxins that bound to specific receptors in their gut, cutting holes in their cell membranes and killing them. The crops killed virtually all of two important insect pests, the European corn borer, *Ostrinia nubilalis*, and the tobacco budworm, *Chloridea virescens*, yet were harmless to most other wildlife and people.

And so, as the best hope of avoiding Bt-resistant insects, entomologists dusted off the old high-dose/refuge theory. They persuaded EPA officials to adopt it. Starting in the late 1990s, whenever the EPA approved a new Bt crop, it also required companies selling those crops to come up with “resistance management plans.” Under these plans, farmers were to keep growing non-Bt crops on some of their land, where insects could avoid exposure to Bt toxins and — hopefully — remain susceptible to them.

Scientists understood that the strategy could fail. In 1998, entomologist Fred Gould, at North Carolina State University, laid out some of its weaknesses in the *Annual Review of Entomology*. He noted that some insects, by virtue of their biology or life cycle, were less susceptible to Bt toxins than others. In those cases, the crop didn’t deliver the “high dose” that the strategy demanded.

In addition, if the planned refuges were too small, or if fewer insects migrated in than expected, less mixing and mating with Bt survivors would occur than the models assumed. There was “high risk,” Gould wrote, that insects would adapt rapidly to Bt crops.

“We told you so”

Gould’s paper made a big impression on Gassmann, then a young graduate student, fueling an interest in Bt crops that has continued ever since. A quarter-century later, he and his fellow entomologist Dominic Reisig, from North Carolina State, returned to the same topic, in the same journal, and reviewed the performance of Bt crops.

Insect ecologists, it appears, can take a bow and say, “We told you so.”

The scientists observed that in cases where Bt crops delivered a highly lethal dose against a pest, and where farmers maintained plenty of non-Bt refuges, the crops met expectations and sometimes exceeded them. In the United States, Bt toxins continue to kill the tobacco budworm and the European corn borer.

Eradication of the pink bollworm became the most spectacular success of all (Tabashnik calls it his “favorite story”). Instead of a refuge, sterile insects were released from airplanes, performing the same function, but with a twist. They didn’t just prevent insects that survived Bt cotton from mating with each other; they ensured that mating would produce no offspring at all.

Elsewhere, though, Gould’s warnings from 25 years ago were borne out. When essential elements of the high-dose/refuge strategy were missing, the miracle crops failed.

In 2003, for instance, Monsanto started selling corn that contained a new Bt gene that killed a particularly damaging pest called the western corn rootworm, *Diabrotica virgifera virgifera*. Yet the crop didn’t deliver one prong of what the theory demanded: a highly lethal dose. This insect is slightly less susceptible to Bt toxins, and some rootworms typically survived, raising the risk that they’d mate with each other.

Some of the EPA’s scientific advisors called for strict limits on the use of this corn. They wanted farmers to plant it in no more than half of their fields, in order to reduce the number of insects that survived exposure to the Bt toxin. Monsanto and some farmers objected to these limits.

The EPA also needed to consider what farmers were willing to do, said an agency official who spoke to *Knowable Magazine* on the condition that he not be identified. “We had to make a determination as to what would actually work.” The EPA eventually decided to let farmers plant rootworm-protected corn on 80 percent of their acreage, the same as permitted in most areas for Bt corn aimed at the European corn borer. When Monsanto later inserted additional anti-rootworm genes into its corn seeds, the EPA allowed farmers to plant them in 95 percent of their fields.

Just six years after the rootworm-protected corn went on the market, farmers started seeing telltale signs of failure. Tall corn plants fell over when the wind blew; closer inspection revealed that their roots had been eaten away. Gassmann collected rootworm larvae from fields and confirmed that they had, indeed, become largely resistant to Bt toxins. Biotech companies introduced several different Bt genes targeting the rootworm, but the insect adapted rapidly to each one.

The western corn rootworm is a devastating pest whose larvae feed on corn roots; if the damage is severe, the plants topple over, as seen in this Iowa cornfield. Credit: Aaron Gassmann

A similar story played out with the western bean cutworm (a corn pest), the destructive fall armyworm and the cotton bollworm (also known as the corn earworm). In each case, the high-dose/refuge strategy didn't work properly, in large part because too many insects survived exposure to Bt crops. Yet the EPA allowed widespread use of these crops and hasn't yet imposed significant restrictions to forestall resistance in those species.

All of these pests have now evolved resistance to multiple Bt genes in the United States and several other countries. In India, where authorities were unable to enforce their own restrictions on planting Bt cotton, the pink bollworm also became resistant. All told, 11 pest species in seven different countries have evolved resistance to nine different Bt toxins.

Whenever a Bt toxin stopped working, seed companies came up with new weapons for farmers to use, often a different Bt gene, producing a different toxin. "Every time you have resistance, [the companies] charge more for a bag of seed with a new trait. So the growers pay," says Reisig, who spends part of his time advising farmers.

The company Bayer, which acquired Monsanto in 2018, said in a statement to *Knowable* that it supports "holistic" approaches to controlling pests that include not just Bt crops, but also judicious use of other tools, including insecticides and crop rotations.

A qualified success

The EPA doesn't have a specific target for how long Bt crops should keep working – just "as long as possible," says the agency official who spoke to *Knowable* on the condition of anonymity. The agency's scientific advisors, he says, once recommended a timespan of at least 10 years. Some Bt crops failed to reach this goal, but the official has few regrets: "I think we did the best we could," he says.

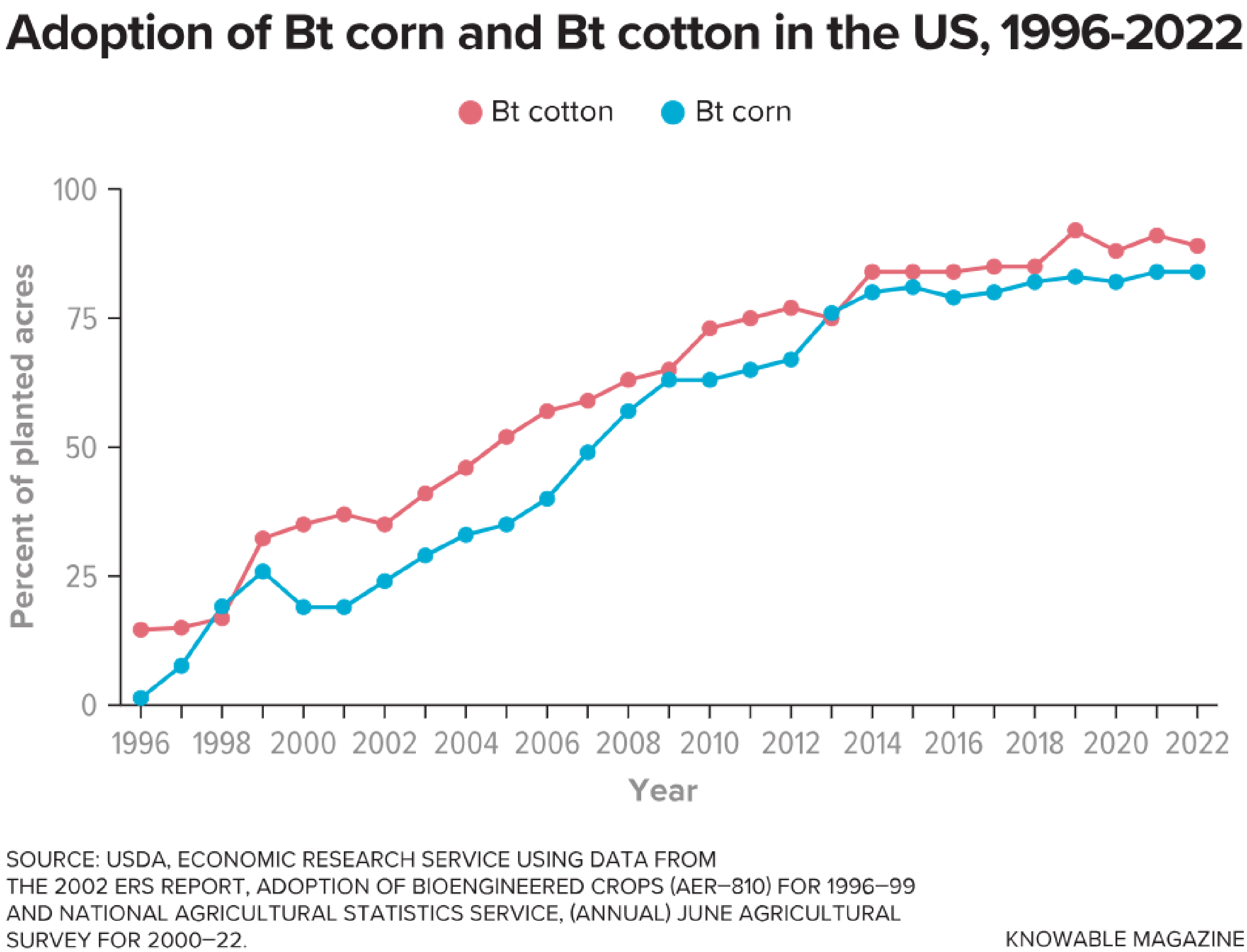
Tabashnik, too, is generally pleased. "Overall, I think Bt crops have been spectacularly successful," he says. Even when insects adapted fairly rapidly, the crops still gave farmers and ecosystems five to 10 years of relief from insect pests and chemical sprays, he says. He's amazed that Bt crops still control the tobacco budworm and the European corn borer. "Most people, including me, thought we'd see resistance to Bt crops really quickly."

Some scientists, though, are bothered to see these unique gifts of nature so quickly used up. "It would have been nice if it could have been used in a way that would have delayed resistance for longer," Gassmann says.

In a way, Bt crops were too user-friendly for their own good. "I think one of the issues is just the convenience," Gassmann says. Farmers loved them. When they worked, they worked miracles, and it was easier to plant insecticidal seeds than to try controlling pests in any other way, including spraying crops with insecticides.

Today, 89 percent of cotton and 84 percent of corn grown in the United States contains genes from Bt, according to the USDA. In areas such as southern states where corn growers are supposed to maintain 20 percent of their fields as non-Bt refuges, they often don't comply with the rules.

"When I surveyed growers in eastern North Carolina, about 40 percent say they plant refuge, and some are not telling me the truth," says Reisig. The reasons, he says, are complicated. Farmers say that they can't obtain good-quality non-Bt corn seed; seed companies say they can't afford to produce non-Bt seed if farmers won't buy it. There's also a more fundamental reason: Farmers simply don't like the idea of leaving some of their fields more vulnerable to insect damage.



Corn and cotton that have been genetically engineered to make Bt toxins are planted widely in the United States. Varieties of these Bt crops that are also engineered to tolerate herbicides are included in the data shown above.

With Bt crops covering much of the landscape, insects are exposed to Bt toxins year after year. In evolutionary terms, it imposes powerful selection pressure, increasing the chances that farmers eventually will find resistant larvae consuming their cotton bolls and ears of corn.

Mexico and Australia offer intriguing examples of better outcomes. Mexico allowed farmers to plant Bt cotton but it has banned the planting of Bt corn, mainly because it does not want to introduce genetically modified corn in the region where the crop first was domesticated and where traditional varieties are often planted. Mexico's cornfields therefore served as an enormous refuge for cotton bollworms, which feed on both cotton and corn. No populations of Bt-resistant bollworm have emerged there.

In Australia, where cotton growers face a related bollworm pest, authorities initially limited Bt cotton plantings to 30 percent of all cotton acreage. Later, cotton that contained just a single Bt gene was taken off the market and quickly replaced with varieties containing two or more; insects are less likely to evolve resistance when confronting plants with such a “pyramid” of Bt genes. Australia’s coordinated resistance management plan, Gassmann says, helped to keep its bollworm susceptible to Bt toxins.

Gassmann says the history of Bt crops teaches the same lesson that entomologists learned from studying chemical insecticides years ago: Insects usually overcome any single weapon that’s overused. He’s pushing for renewed attention to integrated pest management, in which farmers use many techniques to control pests; this can include Bt crops, but also simple ones like rotating crops or nurturing a pest’s natural predators.

The goal is bigger than just extending the useful life of current insect-resistant crops, Reisig adds: It’s to do a better job when the crops of the future come along. And new traits keep arriving as biotech companies race to stay one step ahead of pests. Bayer recently launched cotton varieties containing yet another Bt gene, this one targeting sucking insects like tarnished plant bugs. The company also is deploying corn with RNA sequences designed to interfere with the proper functioning of cells in the corn rootworm.

Yet the Bt experience shows that these tools may prove short-lived. “We’re still doing the same things to stop resistance that we were doing before,” says Reisig, “and we know that it’s going to break.” *Vip3A*, the last Bt gene standing against several insect pests, is showing early signs of breaking. Cotton bollworms that have been exposed to its toxins in the field are tolerating higher and higher doses.

Though measurable crop losses are yet to be recorded, Reisig says, that gene is essentially “gone.”

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