AGRICULTURE

What's holding bioherbicides back

Only a few have been commercialized, but some start-ups say they've cra

by ***Matt Blois***

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Credit: Toothpick Company

A farmer from western Kenya shows a stunted corn cob from a field infested with *Striga* weeds (left) and a healthy corn cob (right) grown on a section of the farm treated with Toothpick Company's fungal bioherbicide.

A few years ago, Peter Nyamgero retired from a career as a computer repair technician in Nairobi, Kenya, and moved to the country to start farming. He bought a 1 hectare (ha) plot near the border with Uganda that hadn't been cultivated for more than 20 years. But soon after planting his first crop of corn, weeds with purple, trumpet-shaped flowers sprouted across his fields.

Seeds from the plant, part of the genus *Striga*, can lie in wait in the soil for decades, germinating only in reaction to hormones secreted by cereal crops. When that happens, they send out tentacles that tap into a host's roots and steal nutrients.

The weeds decimated Nyamgero's plots. "The maize that I planted there . . . they could not reach my shoulder," he says. "That's where they were stopping and were not producing any cobs."

Nyamgero says chemical herbicides weren't very effective against *Striga*, and manually pulling the weeds didn't improve yields either. Then, last year, he heard a radio advertisement about a bioherbicide from Toothpick Company promising to solve his *Striga* problem.

IN BRIEF

For the past few decades, farmers have relied heavily on synthetic herbicides like glyphosate, dicamba, and 2,4-dichlorophenoxyacetic acid to kill weeds. But over time, weeds evolved to tolerate those chemicals, and farmers are struggling to keep them at bay. Several start-ups are now developing herbicides made from fungi, microbial metabolites, or plant extracts to help farmers control these herbicide-resistant weeds. They say their products employ new weed-killing mechanisms to address weeds that chemicals can't eliminate. But bioherbicides face huge challenges. They can be expensive, inconsistent, or narrowly focused on a single weed species.

The quirkily named Kenyan firm had started developing the bioherbicide more than 15 years ago. Using artificial selection, Toothpick scientists coaxed a strain of the fungus *Fusarium oxysporum* that's found only on *Striga* to excrete a combination of amino acids capable of killing the weed. Farmers coat their seeds with the product to create a protective buffer.

The fungus didn't totally eliminate his weeds, but Nyamgero says it suppressed the population enough to boost production from 8 bags of corn per season to more than 20. "I was able to harvest maize normally, as if there were no *Striga* weeds," he says. The company highlights results from farmers like Nyamgero, who started using the seed coating last year, as proof that it works.

> **"I can't retire until I find that darn bioherbicide."**
>
> — ***Pam Marrone,*** *cofounder, Invasive Species Corporation*

Toothpick's fungus is a success in Kenya. Last year, farmers there used it on more than 3,000 ha. But the product is one of only a few bioherbicides to be successfully commercialized. Instead, farmers around the world rely mostly on cheap, chemical herbicides like glyphosate, dicamba, and 2,4-dichlorophenoxyacetic acid (2,4-D) to kill weeds.

That reliance has turned into a problem. Over the last few decades, weeds have repeatedly evolved to tolerate these chemicals, and farmers are now struggling to keep the weeds at bay. Chemical firms have tried to outwit evolution by creating new chemicals that target different plant enzymes than existing products do, but they have **little to show for their efforts**.

In the absence of new chemicals, several start-ups are reexamining bioherbicides made from fungi, microbial metabolites, or plant extracts to help farmers control **herbicide-resistant weeds**. They claim that these biological products employ new weed-killing mechanisms, or modes of action, to

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address weeds that chemicals can't eliminate. But bioherbicides face huge challenges. They can be expensive, inconsistent, or narrowly focused on a single weed species.

Mark Trimmer, president and founding partner of the agricultural biotechnology research firm DunhamTrimmer, says companies are making progress, but it could be years before their products meaningfully displace conventional chemicals. "They are not going to be overnight wonders," he says. "It's going to be a slow development as people learn how to use the products and what to expect from them."

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SLOW GERMINATION

Crop protection firms have long recognized natural molecules as a source of new modes of action that can overcome herbicide resistance. In a **recent report**, the research firm AgBioScout found that companies have discovered at least 250 bioherbicide substances. But they have struggled to turn these substances into products that are cheap and effective.

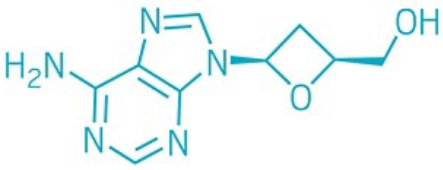
Some of the products are plant oils, like lemongrass or mint oils, that work well as burn-down herbicides. They kill any part of a plant they contact. But Trimmer says they don't persist long enough in a field to stop new weeds from emerging after spraying, and they often need to be applied at such high rates that they're not worth the cost. "They can control what's there today, but they have zero residual activity," he says.

Microbial metabolites are another option. In a **2013 paper** in the *Journal of Chemical Ecology*, a group of scientists from Dow AgroSciences, which was later incorporated into the major US crop protection firm Corteva Agriscience, describes several herbicidal molecules produced by fungi or bacteria. All had problems that precluded commercial viability.

Credit: Toothpick Company

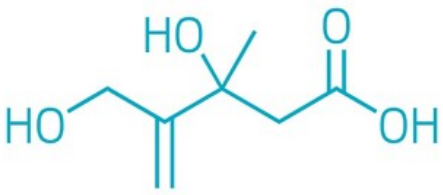
A Toothpick Company employee counts purple-flowered *Striga* weeds in an untreated control plot during a trial of the company's bioherbicide in Homa Bay County, Kenya.

Albucidin, from the bacteria *Streptomyces albus*, could kill broad-leaved weeds, but it took more than 30 days to kill a plant, too slow to be valuable. Macrocidin, a molecule produced by a fungal pathogen found on Canada thistle, showed promising activity on a few members of the Asteraceae family, but it didn't affect other broad-leaved weeds.



Albucidin

The Dow scientists also highlight mevalocidin, a metabolite of the fungi *Rosellinia* and *Fusarium*, as a potentially useful herbicide. It could kill both broad-leaved plants and grasses. Crucially, it appeared to kill weeds using a new mode of action, meaning it would likely be effective against herbicide-resistant weeds. Dow had been granted a patent for the product in 2008, but the **high rates at which the herbicide needed to be applied rendered it uneconomical**.



Mevalocidin

Fungal herbicides have been the most commercially successful. In the 1980s, companies introduced a few fungal products with limited applications. In 1982, Upjohn registered a strain of the fungus *Colletotrichum gloeosporioides* as a bioherbicide for rice and soy farmers. The product is moderately effective, but it hasn't been a breakout success because it doesn't match the performance of conventional chemicals, according to University of Mississippi weed scientist Steve Duke, who authored a **review about the challenges of commercializing bioherbicides** in 2023.

In another notable case, Abbott Laboratories introduced a fungal bioherbicide to kill strangler vine in citrus orchards in 1982. But Duke says the microbe persisted in the ground for so long that farmers could simply get it from their neighbors' soil. The product's efficacy put it out of business. "The lack of success of those two companies sort of scared anybody else off," Duke says.

Since then, other attempts to kill weeds with fungi have mostly stalled. Scientists from Agriculture and Agri-Food Canada, a Canadian government agency, have used the fungus *Phoma macrostoma* to kill a variety of weeds, but production costs are too high for commercialization. The Canadian firm Philom Bios registered a different variant of *Colletotrichum gloeosporioides* to kill round-leaved mallow, but chemical alternatives are cheaper.

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Duke says bioherbicides haven't progressed much in the past 40 years, but he's hopeful that the next decade will be more fruitful. "With the right technology applied to overcome some of these barriers, you could come up with a product . . . that's efficacious, economical, and safe," he says.

HITTING THE TARGET

The ideal herbicide kills a wide variety of weeds but doesn't harm crops or natural vegetation. In the case of synthetic herbicides, crop protection companies have threaded this needle by genetically modifying several major crops to tolerate the chemicals, allowing farmers to spray indiscriminately. It's been much harder to make bioherbicides that achieve the same results.

Fungal herbicides, such as Toothpick's seed coating, are often derived from pathogens that cause disease in plants. Companies developing these products have to show that their fungi kill the weeds they are targeting without infecting the crop a farmer is growing. "It's a narrow window because you're trying to control a weed that is very closely related, in many cases, to the crop," Trimmer says.

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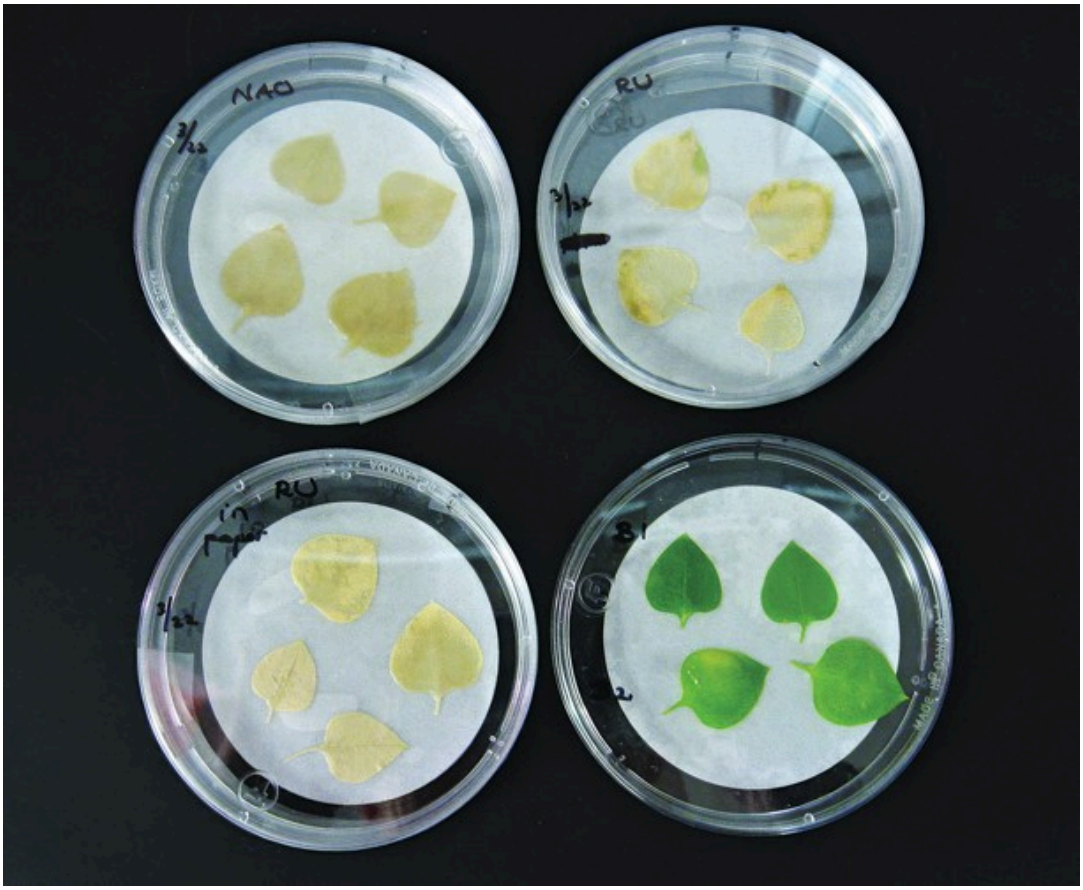

Credit: Invasive Species Corporation

A test by the Invasive Species Corporation compares the herbicidal properties of microbial broths (left-hand containers) with those of a synthetic herbicide (upper-right-hand container). The bottom right-hand dish contains a control weed with no herbicide.

To meet that goal, Toothpick cofounder David Sands, a plant pathologist who led the research on which the technology is based, says the company identified two amino acids, leucine and tyrosine, that inhibited the growth of *Striga* but not corn. His team then selected strains of *Fusarium oxysporum* that produce those molecules.

There's a long list of *Fusarium oxysporum* varieties that infect crops like tomatoes, eggplants, and peppers. As a result, some farmers are wary of this type of weed control. But Sands says each variant tends to affect a single species, and Toothpick used a strain that infected only *Striga* weeds to ensure it wouldn't spread to other plants.

Other fungal herbicides have similarly focused on a narrow range of weeds. The *Colletotrichum gloeosporioides* product developed by Upjohn in the 1980s affected only northern joint vetch, a major problem for US rice farmers. In 2019, US Department of Agriculture scientists used a surfactant to **get the fungus to infect two other rice weeds**, broadening its utility.

Using a host-specific organism makes fungal herbicides safer to deploy, and they may be attractive when a single weed is a major issue. But Deepesh Bista, an agricultural technology analyst with the intelligence firm Lux Research, says an herbicide that controls only a single weed is a tough sell for farmers that have a multitude of weed species in their fields. "I'd rather be using one that gets the job done," he says.

Pam Marrone, a founder of multiple biopesticide start-ups, including Marrone Bio Innovations and the Invasive Species Corporation, says products that exploit a host-specific plant pathogen will always struggle to kill a broad spectrum of weeds. Her strategy is to identify microbial metabolites that are effective against multiple weed species. She favors applying a broth of dead microbes rather than isolated metabolites, which would require expensive purification steps.

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Credit: Jim West/imageBROKER/Shutterstock

Palmer amaranth is one of the most financially damaging weeds in the US. Some populations of the plant have evolved to tolerate more than a dozen types of chemical herbicides.

Marrone Bio Innovations, which was acquired by Bioceres Crop Solutions in 2022, discovered that metabolites from the bacterium *Burkholderia rinojensis* could kill one problematic weed species at low application levels, but the company had to ramp up the level to kill most other weeds, making the product too expensive. But Marrone says it's possible to increase the microbe's production of important metabolites by tweaking the fermentation conditions. "The key to the broad spectrum was getting the cost down," Marrone says.

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In addition to lowering the cost of broadly effective molecules from one microbe, companies can take metabolites from different microbes to achieve the broad-spectrum weed control that many farmers need, Marrone says. But she adds that such an approach is more expensive because it requires more toxicology data.

Marrone Bio Innovations has introduced biofungicides and bioinsecticides. The Invasive Species Corporation has commercialized a product that kills invasive mussels and is moving through the regulatory process for a biopesticide that kills invasive carp. But Marrone continues to search for a bioherbicide that will work on farms. "I can't retire until I find that darn bioherbicide," Marrone said during a panel at the World Agri-Tech Innovation Summit in March.

GreenLight Biosciences is also hoping to make the transition from other pests to weeds. The company recently secured US Environmental Protection Agency registration for a bioinsecticide and is now working on an herbicide. Both products kill pests with small RNA molecules that bind to messenger RNA and stop the production of key proteins.

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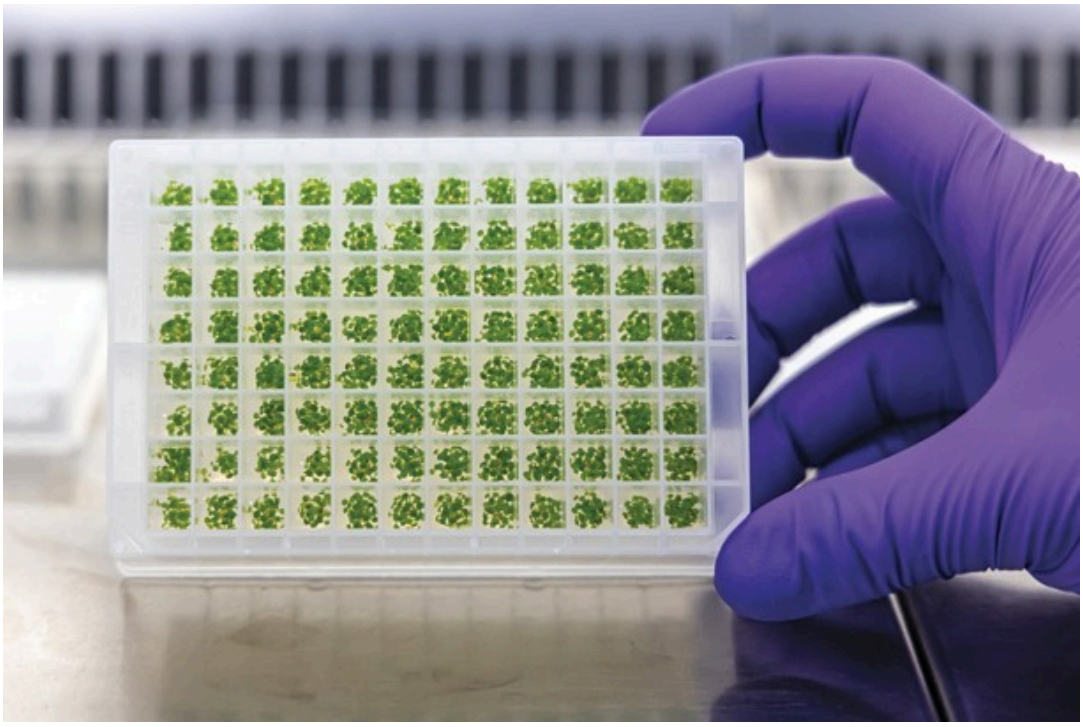
“You can think about it like a lock and key,” says Ron Flannagan, GreenLight Bio’s vice president of research for plant health. “The key will only work on these three species. And that’s because it’s designed at the nucleotide level.”

BETTER TOGETHER

Some bioherbicide companies tout their technology as a path toward an agricultural system free of synthetic pesticides, but others hope to combine their biological products with existing crop chemicals. They say this is the best way to make inexpensive products that can kill multiple types of weeds and still reduce the total amount of synthetic chemicals that farmers use.

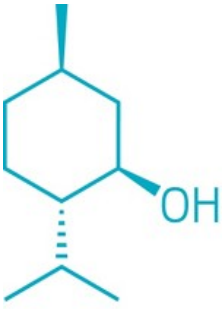


Credit: Moa Technology

Moa Technology uses miniature plants to quickly test the efficacy of new herbicides. The company is searching for both synthetic and biological herbicides that use new mechanisms, or modes of action, to kill plants.

When soybean farmer Phil Christenson was growing up in Nebraska, his father tilled the dirt between rows of crops to remove weeds. After Monsanto introduced RoundUp Ready crops—seeds that had been genetically modified to tolerate the glyphosate-based herbicide RoundUp—in the 1990s, his family and many other farmers switched to chemical weed control.

But as herbicide resistance exploded in the following decades, farmers had to increase the amount of RoundUp they were spraying to achieve the same level of weed control. “RoundUp used to kill everything, and RoundUp was cheap,” Christenson says. “Now, we’re spraying soybeans three, sometimes four times a season. . . . The overall cost of the chemical program is a lot more.”



Menthol

The goal of the start-up Harpe BioHerbicide Solutions is to help farmers like Christenson return to the lower rates of chemical herbicides they used in the 1990s. “It’s not to displace them but to revitalize the chemistries that are struggling,” says Daniel Pepitone, the firm’s chief operating officer.

Harpe plans to combine conventional herbicides that can kill most weeds with a bit of menthol, found in mint, to clean up whatever is left over. Menthol kills plants by making cell membranes leaky, which stops organelles from functioning and halts most

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activity in the cell, like the production of the energy molecule adenosine triphosphate. While most conventional herbicides inhibit a specific enzyme, menthol attacks the entire cell. “It causes the cell to self-destruct,” Chief Technology Officer Chad Brommer says.

Harpe will offer a natural mint oil product for organic farms but plans to use cheaper synthetic menthol in products for conventional farms.

Credit: Harpe Bioherbicide Solutions

A Harpe Bioherbicide Solutions scientist conducts an early-stage study on the effectiveness of a pre-emergent herbicide containing menthol. The company plans to use both natural menthol from mint plants and synthetic menthol in its products.

Harpe’s product can kill kochia plants that have evolved to tolerate glyphosate, dicamba, 2,4-D, and other herbicides. These plants are a major problem for farmers in the US—Pepitone calls them the “hardest weed to kill on the planet.” But menthol also kills crops, so the product can be used only before planting or after harvesting. Harpe is now working with Solis Agrosciences to genetically modify seeds to tolerate menthol, which would allow farmers to use its products during the growing season, similar to the RoundUp Ready system. Harpe says it has already produced a model plant that is resistant to menthol.

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Pro Farm Group, the new name for Marrone Bio Innovations, also expects its bioherbicides to be used in combination with synthetic chemicals. Its first product will use the active ingredient thaxtomin A, derived from *Streptomyces acidiscabies*, a bacterium that infects potatoes. An earlier-stage project continues Marrone’s work on active compounds from *Burkholderia rinojensis*.

Both Pro Farm and Harpe are in the final stages of formulating their first products and say they may be able to seek registration from the EPA by the end of this year.

Louis Boddy, who leads bioherbicide projects at Pro Farm, says the company has already tested its thaxtomin product in combination with glyphosate, glufosinate, and several other chemicals, and it generally performed well. In fact, he says, mixing bioherbicides with synthetic chemicals can make both more effective. Bioherbicides can weaken a plant, giving a chemical herbicide time to find its target enzyme. “They actually help each other out,” Boddy says. “It sort of becomes a one-two punch.”

Many bioherbicide firms see a place for synthetic chemicals. The start-up WeedOUT hopes to prevent the spread of herbicide-resistant weeds by sprinkling them with X-ray-damaged grains of pollen that cause the plants to produce inviable seeds. Ze’ev Weiss, the company’s president, says this nonlethal approach is best used in combination with synthetic chemicals that kill weeds.

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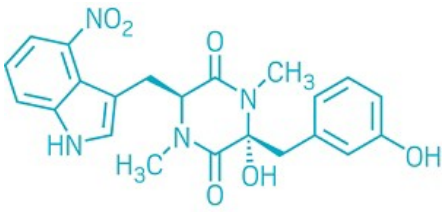
Moa Technology uses high-throughput methods to discover both synthetic and biological herbicides that have new modes of action. In March, the company signed an agreement with Croda to search for bioherbicides in the larger firm's library of compounds from marine microbes. "Using mixtures with synthetics to bring the cost down and make that manageable for the farmers is really important," says Shuji Hachisu, Moa's chief technology officer.



Thaxtomin A

But Boddy says one of the most important arguments for combinations of bioherbicides and synthetic chemicals is that they let farmers do business as usual. It's hard to convince farmers to use a product if they need new equipment or it requires extra work. "You want to ask for as little behavioral change as possible," he says.

NEW SYSTEMS

Companies like Pro Farm and Harpe are committed to creating products that fit into the weed control strategies that farmers already use. But other firms say that the simplicity of systems like RoundUp Ready is what led to the proliferation of herbicide-resistant weeds and that a more sustainable approach to weed control requires a variety of techniques.

Raghavan Charudattan, a plant pathologist and founder of the virus-based bioherbicide company BioProdex, says the one-size-fits-all approach that made chemical herbicides so successful won't work for bioherbicides. He says bioherbicides work best when they are tailored to address a specific problem, like Toothpick's focus on *Striga*. "We have, for far too long, tried to imitate chemical herbicides," he says. "We should move away from the chemical paradigm."

> **"We have, for far too long, tried to imitate chemical herbicides."**
>
> — ***Raghavan Charudattan,*** *CEO, BioProdex*

That will take patience, though. While chemicals with new modes of action have been slow to reach the market, bioherbicides have moved even more slowly. Sands started working on bioherbicides in the 1960s and didn't start selling Toothpick's product until 2021. Charudattan has been in the field for almost as long and also has only one commercial product to his name, but he remains optimistic.

At a **symposium in Puerto Rico** a few years back, Charudattan, Duke, Marrone, and other scientists predicted that farmers would have a much larger toolbox to control weeds by the middle of this century. It would likely include existing chemicals, biopesticides, and synthetic chemicals with new modes of action. They expected that robots would be used to manually pull weeds and that herbicide sprayers would use onboard cameras to identify weeds and spray only where needed, enabling the use of more expensive biological products.

Toothpick cofounder Claire Sands Baker says she sees a place for fungi in the outsize toolbox Charudattan and his colleagues described. Now that Toothpick's product has been commercialized in Kenya, she's hoping to use the technology to tackle weeds in the Americas, a much larger market.

"We're never going to be able to compete with the broad-spectrum, preemergent killers, but maybe that's not the future of farming," Baker says. "They had a really good run for 75 years."

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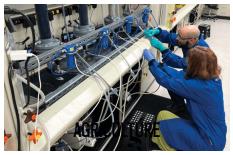

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