Under wraps

Are the crop industry's strong-arm tactics and close-fisted attitude to sharing seeds holding back independent research and undermining public acceptance of transgenic crops? Emily Waltz investigates.

The increasingly fractious relationship between public sector researchers and the biotech seed industry has come into the spotlight in recent months. In July, several leading seed companies met with a group of entomologists, who earlier in the year had lodged a public complaint with the US Environmental Protection Agency (EPA) over restricted access to materials. In a letter to the EPA, the 26 public sector scientists complained that crop developers are curbing their rights to study commercial biotech crops. "No truly independent research can be legally conducted on many critical questions involving these crops [because of company-imposed restrictions]," they wrote.

In turn, the seed companies have expressed surprise at the outcry, claiming the issue is being overblown. And even though the July meeting, organized by the American Seed Trade Association in Alexandria, Virginia, did result in the writing of a set of principles for carrying out this research, the seed companies are under no compunction to follow them. "From the researchers' perspective, the key for this meeting was opening up communication to discuss the problem," says Ken Ostlie, an entomologist at the University of Minnesota in St. Paul, who signed the complaint. "It will be interesting to see how companies implement the principles they agreed upon."

What is clear is that the seed industry is perceived as highly secretive and reluctant to share its products with scientists. This is fueling the view that companies have something to hide.

Who's in control?

It's no secret that the seed industry has the power to shape the information available on biotech crops, referred to variously as genetically engineered or genetically modified (GM) crops. Commercial entities developed nearly all of the crops on the US market, and their ownership of the proprietary technology allows them to decide who studies the crops and how. "Industry is completely driving the bus," says Christian Krupke, an entomologist at Purdue University in West Lafayette, Indiana.

Company control starts with a simple grower's contract. Anyone wishing to buy transgenic seeds has to sign what's called a technology stewardship agreement that says, among many things, that the buyer cannot conduct research on the seed, nor give it to someone else for research. This means scientists can't simply buy seeds for their studies, and farmers can't slip them some on the side. Instead, scientists must get permission from the seed companies or risk a lawsuit. "You need permission from industry and you have to specify what you want to do with the plants," says Bruce Tabashnik, an entomologist at the University of Arizona in Tucson.

Seed companies can refuse a research request for any reason, and they get fairly inventive. In 2002, Paul Gepts, a plant geneticist at the University of California, Davis, wanted to check for the presence of transgenic maize in Mexican households after reports that DNA from GM maize had transferred to local varieties. He requested seed samples from three companies, explaining that he wanted to compare them to the seeds from the Mexican households to see if they contained the same genetic material. "I thought naively that that would be a courtesy and I could get a small sample. But they didn't really want to do it," Gepts says. According to emails reviewed by *Nature Biotechnology*, Monsanto, based in St. Louis, told Gepts to get a powder sample from Europe, which didn't work well for the experiment, Gepts says. Gan-Yuan Zhong, a researcher at the time at Johnston, Iowa–based Pioneer Hi-Bred, told Gepts that the company didn't have the "appropriate material" to share. And Syngenta, in Basel, suggested Gepts collaborate with the Mexican government, which was investigating the issue.

How often these kinds of rejections are happening is unclear. Some may be isolated instances; others result from company policies. For example, Syngenta recently implemented a rule prohibiting any study that compares its commercial crops to other companies' crops, according to Paul Minehart, a spokesperson for Syngenta. One scientist affected by the change, Minnesota's Ostlie, wanted to compare how three companies' insect-resistant corn varieties fared against local species of rootworms. All three products had been commercialized, and Syngenta, Monsanto and Pioneer gave Ostlie permission to do the study for the 2007 growing season. But for the 2008 season, Syngenta backed out. "In late 2007, we changed our policies on research," says Minehart. "We decided not to get involved in any comparison studies," he says. Many Syngenta products contain components licensed from other companies, and Syngenta has agreements with those companies that they won't compare their products, Minehart says.

Unavailable for testing. Independent researchers have their hands tied when it comes to testing commercial GM crops.

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The idea of having to get permission from companies to do studies is a deterrent in itself. "There are three strategies that people take," says Elson Shields, an entomologist at Cornell University in Ithaca, New York. "Some are just not doing the research. Some are changing their experimental protocols so that they are acceptable to industry—which may or may not be a good thing," he says. "And some are just going out and buying the seeds and doing the research in violation of the technology agreements."

Requesting permission from the companies can be daunting. The requester usually has to describe in detail the design of the experiment—information scientists may not want to divulge. Some researchers object to revealing their hypotheses because it provides companies with a head start in preparing a rebuttal.

Once the company and the scientist agree on the design, they must negotiate the terms of the research agreement. Negotiations tend to break down when companies want to limit or control publication of the study. "When you are funded by state and federal dollars, you have an obligation that the research you conduct is public and published," says Beverly Durgan, dean of extension services at the University of Minnesota. "So signing research secrecy agreements is something we really can't do," she says. The US Department of Agriculture's (USDA) research arm, Agricultural Research Service (ARS), has a similar policy. "We can sometimes agree to some limitations on publishing like having the company review the results X days before publication," says Kalpana Reddy, in the office of tech transfer at ARS. "But we won't agree to any sort of blanket approval, which would limit our right to publish."

Negotiations in 2008 between Monsanto and two universities—North Dakota State University and the University of Minnesota—broke down when Monsanto insisted on approving publication of any data on its newly commercialized transgenic sugar beets, according to Durgan. The university had proposed "the general type of research our faculty would conduct with any new crop variety," she says. "Monsanto wanted the right to approve all publications, and we said that was not possible," she says. As a result, no sugar beet research was conducted by Minnesota or North Dakota State University in the 2008 growing season. A Monsanto spokesperson claims that "it became necessary to manage research agreements more carefully" when separately, Monsanto's sugar beet became an object of litigation. Monsanto and the two universities came to a compromise for the 2009 growing season.

Studying crops hasn't always been this difficult. "Before biotech came around, when new varieties came out, local groups would get together and have a local trial," says Alan McHughen, a plant biotechnologist at the University of California, Riverside. Crop clubs, composed of local farmers and university scientists, would do agronomic studies to see which varieties perform best and how they interact with the local environment. "If it was okay in the past, I don't see why companies would object to it now," says McHughen.

Most major seed companies seem to have made an effort to enable scientists to do such agronomic research. Pioneer, Monsanto, Syngenta and Indianapolis-based Dow AgroSciences say they have negotiated multi-year agreements with major universities that give those scientists the freedom to conduct and publish most agronomic research without having to get permission from the company for every study (**Box 1**). But the limits of these agreements are often unclear. A group at Penn State generated a list to "put in front of companies to find out what kind of research falls under these agreements," says Dennis Calvin, an entomologist at the university.

The new principles drafted by the seed trade association this summer may help clarify, and possibly expand, these limits. The group aims to finalize the draft by the end of the year.

Box 1 Limited-use licenses

Filtering through research requests can become unwieldy for companies. Pioneer, for example, has 11 people on staff whose sole job is to facilitate seed requests, says spokesperson Pat Arthur. So most major seed companies have a system in place with universities that allows academic scientists to do certain agronomic studies without having to get permission from the company for each study. For example, since 2002 Monsanto has distributed a broad academic research license to over 150 universities and research institutions, which allows research on commercial crops "to supply agronomic information," according to a copy reviewed by *Nature Biotechnology.* Research results can be published and discussed publicly.

Examples of "agronomic" research allowed under the license include experiments on weed management systems, insect management systems, tillage methods and variety performance—the kinds of things farmers would want to know when planting a new crop. Studies outside of agronomic research—breeding, reverse engineering or characterizing the genetic composition—require a separate, formal research agreement with Monsanto.

Nearly all the scientists *Nature Biotechnology* spoke with either did not know about Monsanto's limited-use license, or were unclear on what they would be allowed to do under the license. "That tells us that we haven't done as effective a job as we could in communicating that they have this license and the freedoms they have to conduct research," says Sachs at Monsanto. The July meeting between the seed companies and the public sector entomologists may spread the word about the existence of these kinds of agreements, says Ostlie.

Keeping tabs

Industry spokespeople say they were surprised by the scientists' complaint to the EPA. "It's clear that academics have an issue that needs some attention," says Eric Sachs, director of global scientific affairs at Monsanto, who attended the July meeting. "But some scientists we've talked to think this issue has been blown way out of proportion," he says. "The language in that letter seemed to suggest that some products on the market may very well be unsafe because they haven't been adequately tested. That's going too far in my mind," he says.

The companies say they have to keep tabs on public sector research because they want to make sure the studies are done with good stewardship practices and in accordance with regulations. If there is an adverse event with a precommercial product, seed makers could be liable, even if the event occurred under the watch of a public sector scientist. Any adverse events with commercial products have to be reported to regulatory authorities as well. Industry spokespeople also say they want to be mindful of the integrity of US grain exports so that products that haven't received approval in some countries aren't sent there.

Companies also want to protect their intellectual property (IP) and their investment in the product. They are particularly averse to allowing the public sector to breed crops or to characterize the genetic composition of the plant. After all, a biotech crop can cost up to $100 million to develop, according to industry estimates. "Where would you stand if this were your product?" asks Carol Mallory-Smith, a weed scientist at Oregon State University in Corvallis.

And, companies want the studies done right. "If you do some poorly organized research proposal, a company might not be inclined to give you the seeds because they're afraid it won't

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cast a favorable light on their product," says Rick Goodman, a food scientist at the University of Nebraska-Lincoln and a former Monsanto researcher. "The consequences can be huge," he says. Biotech crops are intensely scrutinized, and any negative study that comes out tends to be widely disseminated by vocal anti-GM groups. Companies have spent countless hours defending themselves from such groups. "Critics are looking for any little problem with the technology," adds Tabashnik.

Industry spokespeople say they want strong relationships with academics because they depend on their expertise. In fact, seed companies frequently pay academics to study precommercial products, similar to consulting arrangements or discovery work carried out in academia for big pharma. Monsanto, for example, will pay anywhere from a couple thousand dollars to do a single-field study to a couple hundred thousand dollars to do more complex laboratory work or an animal feeding study. "If industry wasn't sponsoring this research there would be much fewer data than there is now," says Blair Siegfried, an entomologist at the University of Nebraska-Lincoln.

Shoddy studies?

A potential check on industry's control over the data is the role that regulatory agencies play on product approval. But some scientists worry that these agencies aren't asking for the right safety tests. "Companies put in mountains of data but there's no devil's advocate—no other side," says Krupke at Purdue.

In the US, under the Federal Food, Drug and Cosmetic Act of 1938, the FDA is responsible for ensuring that food is safe to eat, although by statute, it regulates only food additives. By that definition, most crops are exempt from FDA approval, although companies tasked with ensuring their products are safe often voluntarily submit a considerable amount of information. Certain types of commercialized crops also fall under the jurisdiction of the USDA and the EPA: the USDA is concerned with minimizing gene flow, the EPA regulates crops containing pesticides, such as those with insect-resistance traits. Transgenic and conventional crops with other traits—herbicide tolerance or nutritional enhancement—could enter the marketplace with almost no review of the potential health impacts[1]. The EPA also regulates unintended effects on nontarget insects, although a review of published studies identified problems that limit their usefulness[2,3].

The fact that much of the data submitted to regulatory agencies remains confidential business information that is not shared with the research community means that for many crops (transgenic or otherwise), little information on human or environmental toxicity is known. Certainly, there is a paucity of such studies in the literature. Spanish researcher Jose Domingo, at Rovira i Virgili University in Reus, conducted a literature review of toxicity studies conducted on commercialized GM crops. So few research papers turned up in his search that he asked, "Where is the scientific evidence showing that GM plants/food are toxicologically safe?"[4].

In some instances, university scientists have raised concerns about data submitted to regulatory agencies, but had no recourse. In 2001, for example, Pioneer was developing a transgenic corn variety that contained a binary toxin, Cry34Ab1/Cry35Ab1, to fend off rootworms. The company asked some university laboratories to test for unintended effects on a lady beetle. The laboratories found that nearly 100% of lady beetles that had been fed the crop died after the eighth day in the life cycle. When the researchers presented their results to Pioneer, the company forbade them from publicizing the data. "The company came back and said 'you are under no circumstances able to publicize this data in any way'," says a scientist associated with the project, who asked to remain anonymous. Because the product had not yet been commercialized, the research agreement gave Pioneer the right to prevent publication of their results.

Two years later, Pioneer received regulatory approval for an antirootworm corn variety with the same toxin—Cry34Ab1/Cry35Ab1. But the data submitted to the EPA had no sign of potential harm to lady beetles, even though Pioneer had followed common EPA testing protocols. In one study, the company fed purified toxins to the lady beetles only through the seventh day of their life cycle—one day short of what was found to be their most susceptible stage. In a second study, the company followed the lady beetles through the end of their life cycle but used a different mode of feeding, through a homogenized powder consisting of half prey and half pollen, and didn't see any effect, according to Jim Register, a scientist at Pioneer. Register also says that although Pioneer's commercialized product contains the same toxin as the one the universities studied, it is a different construct—key genes were integrated into a different place in the genome.

The anonymous researcher maintains that Pioneer's studies are flawed. The EPA was made aware of the independently produced data, but opted not to act, according to the anonymous source. Pioneer would also not give the scientists permission to redo the study after the crop was commercialized.

Scientists can in theory review the data companies file with regulatory agencies. "Independent scientists mostly want to review the data to see if it's good science or regulatory junk science and also to conduct their own research," says Bill Freese, an analyst at the Center for Food Safety in Washington, DC. But roadblocks exist to this as well. Scientists have to submit Freedom of Information Act (FOIA) requests, which can take months, and allows access only to information that is not confidential business information. In this regard, the USDA has been accused by a National Academy of Sciences committee of allowing companies to make excessive claims of confidential business information[5].

Companies have been known to take the confidentiality of data on their GM crops to even greater extremes. Tabashnik says a Dow AgroSciences employee once threatened him with legal action if he published information he received from the EPA. The information concerned an insect-resistant variety of maize known as TC1507, made by Dow and Pioneer. The companies suspended sales of TC1507 in Puerto Rico after discovering in 2006 that an armyworm had developed resistance to it. Tabashnik was able to review the report the companies filed with the EPA by submitting a Freedom of Information Act request. "I encouraged an employee of the company [Dow] to publish the data and mentioned that, alternatively, I could cite the data," says Tabashnik. "He told me that if I cited the information...I would be subject to legal action by the company," he says. "These kinds of statements are chilling."

Many think that companies aren't helping their image with these strong-arm tactics and a close-fisted attitude to materials sharing. The industry has taken a lot of hits over the years, particularly from activist groups ready to pounce on any sliver of anti-GM information. "If there's a sense that a problem is being swept under the carpet, then that only fuels the fear," says Tabashnik. "I think it's better to be open about it," he says. "It's not as if one problem with one variety means the whole technology isn't useful."

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