

Glyphosate resistance threatens Roundup hegemony

Weeds are becoming increasingly resistant to glyphosate, a report from the US National Academy of Sciences (NAS) released in April has found. The driving force, according to the report, is farmers' dependence on the weed killer accompanied by the widespread adoption of genetically modified (GM) herbicide-tolerant crops. Seed makers are hoping to forestall the problem by developing GM crops with 'stacked' traits that tolerate multiple herbicides. But weed scientists warn that if farmers manage these new crops in the same way as they managed their glyphosate-tolerant predecessors, weeds will simply become resistant to the new technologies.

"The number of weed species evolving resistance to glyphosate is growing," the report says. At least eight weed species in the US have become resistant to glyphosate, and the trait is prevalent in areas where farmers grow crops that have been genetically engineered to resist the weed killer. The authors are calling for "national attention" to the weed problem.

Glyphosate was first commercialized in 1974 by St. Louis -based Monsanto under the brand name Roundup. It became a key weed control tool for farmers in 1996 when Monsanto developed a GM soybean variety called Roundup Ready that expresses a gene encoding enol pyruvate shikimate-3-phosphate synthase from the microbe *Agrobacterium tumefaciens* conferring tolerance to the herbicide. Growers loved it. Roundup killed a broad array of weeds without killing their Roundup Ready soybeans. Seed makers went on to commercialize glyphosate-tolerant corn, cotton, canola and sugar beets. After Monsanto's patent on Roundup expired in 2000, companies commercialized dozens of glyphosate formulations. "We have found something that really works, and we have really used it," says William Johnson, a weed scientist at Purdue University in West Lafayette, Indiana.

The system was so convenient that growers began relying exclusively on glyphosate for weed control—a recipe for resistance. "Glyphosate had been used forever, so people were not as cautious," says Yves Carrière, an author of the report and an entomologist at the University of Arizona in Tucson. The first report of glyphosate resistance associated with a GM glyphosate-tolerant crop came in 2000 in Delaware in a species of horseweed. Since then, a new resistant weed species has been reported nearly every year in the US and South America. Glyphosate resistance has also been reported in Australia, South Africa, Europe, China, Malaysia and Canada.

Glyphosate isn't the only herbicide facing resistance from weeds. At least 195 weed species have evolved resistance to 19 herbicides, accord-

ing to the NAS report. Glyphosate, however, is one of the most economically important. In the US alone, over 90 million pounds are used annually, and it is the number-one-selling herbicide worldwide.

Biotech seed makers are responding to the problem by developing new herbicide-tolerant crops (Table 1). "The strategy is that the crops would be tolerant to two or more herbicides," says John Soteris, global weed resistance management lead at Monsanto. The hope is that the crops will allow growers to use a wider variety of herbicides and weed control practices. For example, if a crop is tolerant to both glyphosate and glufosinate, a farmer could alternate the herbicides, or use them in combination. The most likely candidates for development, according to the NAS report, are genes that confer resistance to herbicides such as dicamba, glufosinate, hydroxyphenylpyruvate dioxygenase (HPPD) inhibitors, 2,4-D and other synthetic auxins, acetolactate synthase (ALS) inhibitors and some acetyl-CoA carboxylase (ACCase) inhibitors. Most companies are focused on combining one or two of these traits with glyphosate tolerance. "You don't want to throw out glyphosate completely," says Nicholas Storer, a global science policy leader for biotech at Dow AgroSciences in Washington, DC.

But some scientists say the next generation of GM crops will only buy growers more time until another group of weeds evolves resistance. "This is an incredible technology that is being compromised because of farm management decisions and there is nothing in the pipeline that is going to fix that," says Michael Owen, an author of the NAS report and a weed scientist with Iowa State University in Ames. Purdue's Johnson predicts that it will take 7 to 9 years for some weeds to evolve resistance to the next generation of herbicide-tolerant crops, if the new technologies are adopted with the same celerity as Roundup Ready.

Because technology alone won't solve the weed problem, companies in recent years have "taken up the banner for stewardship," says Owen. "As scientists, we can't prevent resistance to any herbicide, and that being the case, it comes down to basic farm management," adds Monsanto's Soteris. The company provides educational materials to growers through sales meetings, technical use guides and websites (e.g., <http://www.weedresistancemanagement.com/>). The materials encourage crop rotation and the addition of a nonglyphosate herbicide to their weed control program—recommendations that fall in line with messages from university extension scientists and the NAS report. "What



These marestail plants infesting a crop of wheat in Tennessee are resistant to glyphosate herbicide Roundup.

we're preaching is that a diversified program is needed," says Soteris. "To rely on a single herbicide exclusively can lead to resistance."

Monsanto hasn't always taken that stance, however. "Monsanto had a very aggressive marketing campaign in the late 1990s saying that weeds would not develop resistance if [growers] used herbicides at the right time and at the right rate," says Johnson. "They told users that the resistance mechanisms were very complex, not commonly found in plants grown in the wild, and difficult to insert into the crop," adds Carol Mallory-Smith, a weed scientist at Oregon State University in Corvallis, "Monsanto discouraged the use of other herbicides in the system." For example, to qualify for Monsanto's 'Roundup Rewards' program—a kind of warrantee for crops—growers in the late 1990s could only use Roundup and certain approved herbicides on Roundup Ready crops. The company has since changed the qualifications for its rewards program.

A spokesperson for Monsanto says the company has "never restricted the use of nonglyphosate herbicides in Roundup Ready crops" but that the company also did not initially promote weed control programs that included other herbicides. "Based on what we knew in the early years, we believed our recommendations were appropriate," says Eric Sachs, director of global scientific affairs at Monsanto.

IN brief

SBIR grants wax

Awards under the Small Business Innovation Research (SBIR) program have just been given a boost. As of March 30, the cap for SBIR phase I awards has risen from \$100,000 to \$150,000, and for phase II awards from \$750,000 to \$1,000,000. The increases are intended to take account of inflation since 1992 when the threshold amounts were last set by Congress. "This will have an important positive impact at a critical [juncture] in the aftermath of the nation's great recession," says Simcha Jong, university lecturer in management science and innovation at University College London. Jong says that, historically, the SBIR program helped forge links between university science and industry and, at this pivotal time, could help kick-start the US job engine. The Senate has passed a bill to extend the SBIR and related Small Business Technology Transfer through July 31 (*Nat. Biotechnol.* **27**, 1065–1066, 2009). Even more generous than SBIR grants are the new Small Business Helping Investigators to Fuel the Translation of Scientific Discoveries (SHIFT) awards launched on March 5 by the US Department of Health and Human Services. These awards, aimed at fostering translational research, offer companies up to \$2.65 million over five years. "The main point is to encourage current academic researchers to apply, and use it to move to biotech," says Jiwu Wang, president and CEO of Allele, a San Diego-based company that has taken products to market with SBIR support. "It is a great idea." *Emma Dorey*

Relief over stem cell lines

The US National Institutes of Health (NIH) announced the addition of 13 lines to its Stem Cell Registry. The news was cheered by the research community, as the two most widely studied lines—H7 (WA07) and H9 (WA09) owned by the WiCell Research Institute of Madison—were included in the batch approved by NIH director Francis Collins. The total number of NIH-approved human embryonic cell lines in the registry, and thus eligible for federal funding, has risen to 64 as of April 29. These recent approvals ease frustrations among scientists who watched President Obama's March 9, 2009 Executive Order—welcomed at the time and intended to remove barriers for such research—later backfire when NIH insisted that cell lines used during the George W. Bush presidency be reevaluated under revised ethical guidelines that NIH began following in July 2009 (*Nat. Biotechnol.* **27**, 681, 2009). Playing down the vociferous complaints since then, Collins says the approvals this April should enable researchers to "continue their studies without interruption, and we can all be assured that valuable work will not be lost." Even though Collins seems to discount projects that were disrupted during that interval, NIH-supported human embryonic stem cells research now is poised to get back on track. The H7, H9 and other recent approvals are indeed a "huge relief," says bioethicist Christopher Scott, who directs the Program on Stem Cells and Society at Stanford University. *Jeffrey L. Fox*

Table 1 Selected crops in development tolerant to two or more herbicides

Company (location)	Crop	Herbicides tolerated
Bayer CropScience (Monheim am Rhein, Germany)	Soybean	HPPD inhibitors, glufosinate, glyphosate
	Cotton	Glufosinate, glyphosate
Dow Agrosciences	Corn	Phenoxy auxins (e.g., 2,4-D), aryloxyphenoxypropionate ACCase inhibitors (e.g., quizalofop-p-ethyl), glyphosate
	Cotton, soybean	2,4-D, glyphosate
	Corn, cotton	Dicamba, glufosinate, glyphosate
Monsanto	Soybean	Dicamba, glyphosate
	Corn	Dicamba, glufosinate, glyphosate
Pioneer Hi-Bred (Johnston, Iowa)	Corn, soybean	ALS inhibitors, glyphosate
Syngenta (Basel)	Soybean	HPPD inhibitors (e.g., mesotrione), glufosinate, glyphosate

HPPD, hydroxyphenylpyruvate dioxygenase; 2,4-D, 2,4-dichlorophenoxyacetic acid; ACCase, acetyl coenzyme A carboxylase; ALS, acetolactate synthase.

Despite the recent efforts by companies and continued efforts by university scientists, the message to 'diversify' doesn't always stick with growers. According to the NAS report, growers are reluctant to stop using glyphosate even when facing signs of resistance in their fields. "For controlling problematic weeds, [growers] prefer increasing the magnitude and frequency of glyphosate applications, using other herbicides in addition to glyphosate, or increasing their use of tillage," the authors of the report wrote. A 2009 survey sponsored by Monsanto found that >75% of farmers were aware of the potential for weeds to develop resistance to glyphosate. But less than half of those farmers said they believed that rotating crops and alternating herbicides would be effective practices for minimizing weed resistance.

Growers can't be legally forced to reduce their glyphosate use. Unlike pesticide use, herbicide use is not regulated by the US federal government. Regulations wouldn't be practical anyway, says Owen. "It can't be done in a way that would keep resistance from evolving," he says. "The impossible part would be enforcing the regulations."

Weed scientists say they hope that the NAS report will at least raise awareness among the general public about the weed resistance problem. The 253-page report also emphasized that insect-resistant crops help farmers reduce pesticide use, and found that overall, "planting of [genetically engineered; GE] crops has largely resulted in less adverse or equivalent effects on the farm environment compared with the conventional non-GE systems that GE crops replaced."

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BIO's beastly bugs

When was the last time someone called *E. coli* cute? Many did at this year's Biotechnology Industry Organization (BIO) Annual Meeting in Chicago where conference goers were treated to a collection of giant fuzzy microbes courtesy of biomanufacturers SynCo Bio Partners. MRSA or HIV anyone?



IN their words



"Science is not a 100-yard dash. It is a marathon—a marathon run by a relay team that includes researchers, patients, industry experts, lawmakers and the public." While testifying to a congressional subcommittee NIH Director Francis Collins

stresses the long timelines involved in translating \$32.2 billion of proposed funding into products. (*GenomeWeb News*, 28 April 2010)

"We've been selling it since 1998, probably 200 million pounds from Honolulu, and not a single bad case of anything going wrong." Papaya farmer Ken Kamiya makes the case for transgenic papaya recently approved in Japan, where a single papaya can fetch \$10. (*Honolulu Advertiser*, April 25 2010)

"The worst case of corporate bullying I've ever seen." Attorney Ray Chester on Botox producer Allergan's (Irvine, CA) campaign to recover \$460,000 in legal costs from Dee Spears, who unsuccessfully sued the drugmaker over the death of her 7-year old daughter with cerebral palsy who had received the treatment. (*Orange County Register*, 20 April)