1 April 2019

The Registrar: Genetically Modified Organisms Act
Private Bag X973
Pretoria 0001
Email: GMOAppComments@daff.gov.za

On behalf of the Pesticide Action Network North America (PANNA), I respectfully submit the following comments to urge the government of South Africa to reject Corteva (formerly Dow Agrosciences) application for commercial release of three maize varieties, genetically engineered to withstand applications of the herbicide, 2,4-D.

PANNA is a non-profit, public interest organization representing the concerns of over 100,000 supporters across the United States, including farmers, farmworkers, health professionals, members of sustainable agriculture, labor, environmental and consumer groups and individuals concerned with the safety, sustainability, fairness and integrity of our food and agricultural system. PANNA is part of the PAN International network, established over 35 years ago, with the PAN Africa regional center located in Senegal.

Based on the threats that Corteva/Dow's 2,4-D herbicide and its 2,4-D-resistant seeds pose to farmers' livelihoods and the health and well-being of rural communities, PANNA strongly urges South Africa to avoid the mistakes made in the US, and reject Corteva/Dow's petitions for approval of its 2,4-D-resistant maize varieties.

If South Africa approves these seeds, vast acreages of farmland are likely to be negatively impacted, as will the health and livelihoods of rural communities. South Africans will witness not only a tremendous increase in application of the hazardous herbicide, 2,4-D, but also the swift evolution of weed populations resistant to 2,4-D, creating additional costs and severe challenges to farmers already struggling to make ends meet.

Furthermore, the likelihood of 2,4-D drift (whether by mechanical spray drift from the newer formulation or both mechanical and volatilization drift from older cheaper formulations which will likely still be used) threatens farmers with severe crop damage. Organic farmers would suffer not only yield loss but also potential loss of organic certification of their crops as well, resulting in further economic hardship across the agricultural sector.

Below we outline in greater detail the health, economic and livelihood harms that introduction of 2,4-D-resistant seeds would likely bring to South African farmers and rural communities, as well as the existence of more promising ecological alternatives in weed management that make reliance on herbicide-resistant GMO seeds unnecessary.

Herbicide use will increase

Of relevance to the South African government's decision are the findings of our own US agencies and scientists regarding the estimated increase in herbicide use. The US Department of Agriculture (USDA) Environmental Impact Statement (EIS) acknowledged that introduction of 2,4-D resistant crops would drive up use of 2,4-D in the U.S. by 200-600%, over a 10 year period (USDA EIS, p. 4-34).[1] Independent scientists in the US have calculated a

20-fold increase in corn in just 5 years, should 2,4-D crops be commercialized here.[2] Regardless of differences in model assumptions , the consensus is clear: 2,4-D use will rise dramatically over several years once 2,4-D resistant seeds are approved. *The same impact would certainly be experienced in South Africa.*

Pesticide drift will increase

2,4-D is a highly volatile herbicide that is prone to drift beyond the field of application to damage neighboring crops and wild plants. The American Association of Pesticide Control Officials reports that **2,4-D is the herbicide most responsible for drift-related crop injury**.[3] The USDA EIS stated that with introduction of 2,4-D resistant maize, 2,4-D applications would be likely to occur over a longer period of time and **throughout warmer weather when volatilization risk increases**. The USDA also acknowledged that the agency was unable to accurately predict the degree of drift damage likely to occur.

While Dow claims that its new formulation of 2,4-D (known as "Enlist") is less prone to volatilization drift, this new formulation merely reduces and does not eliminate *volatilization drift*. Furthermore, *mechanical spray drift* of both new and old product formulations remains a continuing and serious threat to non-2,4-D resistant maize and other vulnerable crops growing on neighboring farms. As well, the availability of older, *cheaper and highly volatile* "DMA" formulations creates an additional market incentive to cut costs, which few farmers are able to resist.

Crop damage from herbicide drift will occur

2,4-D vapor injures most broadleaf (i.e. non-grass) plants at extremely low levels, as low as three-billionths of a gram per liter of air.[4] Particularly sensitive crops include grapes,[5] tomatoes, cotton,[6] soybeans, sunflower, lettuce, cabbage, strawberries, peppers, squash, beans, peas among others—in other words, virtually all fruits and vegetables.

Two surveys by US state pesticide regulators established that 2,4-D drift is already responsible for more episodes of crop injury than any other pesticide.[7] Introduction of 2,4-D-resistant crops will greatly increase use and hence drift injury to crops and wild plants — including endangered species, adjacent ecosystems and entire landscapes —by enabling higher and more frequent application rates, on much greater hectarage, sprayed throughout and later in the season when neighboring crops and plants have leafed out and are thus more susceptible to drift injury.[8]

Through the volatilization process, 2,4-D can "leapfrog" its way for miles by volatilizing during the heat of day, traveling in a gaseous state, condensing at night and landing on and damaging crops (as well as non-crop plants), then re-volatilizing the next day and spreading harm further and further. In the US, 2,4-D has volatilized and drifted as far as 100 miles from application site, damaging fruit orchards along the way and ultimately wiping out 15,000 acres of cotton.[9]

Conventional farmers are likely to lose crops while organic farmers could lose both crops and organic certification, resulting in an economic unraveling of already-stressed rural communities. In response, family farmers and processors in the U.S. formed the Save Our Crops Coalition to oppose 2,4-D crops, which pose a threat to their economic survival.[10]

Crop losses associated with 2,4-D drift would likely harm **South Africa's export markets, farmers' economic survival** and **home production necessary for food security**.

Health risks from 2,4-D exposure will increase

The expected increase in use of 2,4-D is also likely to pose adverse health risks for farmers, women, children and rural communities. 2,4-D is known to be a hormone-disrupting chemical, which can affect critical developmental processes in very small amounts. Lactating rats fed low doses of 2,4-D exhibit impaired maternal behavior while their pups weigh less.[11] Children of pesticide applicators in areas of Minnesota with heavy use of chlorophenoxy herbicides like 2,4-D had a disproportionately higher incidence of birth anomalies than in non-crop regions or where these herbicides were less used.[12] 2,4-D is frequently detected at low levels in surface water,[13] levels certain to rise sharply with introduction of 2,4-D corn.

Medical research shows that farmers suffer higher rates of certain cancers, such as non-Hodgkin's lymphoma (NHL), a cancer of the lymph nodes that kills 30 percent of those afflicted.[14] Numerous epidemiology studies in Sweden,[15] Canada,[16] and by scientists at the U.S. National Cancer Institute[17] have found that farmers who use 2,4-D and related herbicides are more likely to contract deadly NHL. Sweden, Norway and Denmark have banned 2,4-D based on such studies. The U.S. National Academies' Institute of Medicine has consistently found "sufficient evidence of an association between exposure" to Agent Orange chemicals, which include 2,4-D, and NHL.[18] Other studies link farmer 2,4-D exposure to higher rates of Parkinson's Disease.[19]

Please see attached letter to the US Environmental Protection Agency (EPA), signed by 70 physicians, nurses, public health scientists and other health professionals, outlining serious health concerns associated with 2,4-D exposure that have been documented in the scientific literature, and urging the denial of Dow's application for approval of 2,4-D to be used on its 2,4-D resistant seeds.

Health risks associated with Dow's 2,4-D resistant crops include exposure to glyphosate

The health risk that South African communities would face from introduction of Dow's herbicide-resistant GMO maize does not stop with 2,4-D. *Enlist Duo*—the herbicide product designed to be used with Dow's Enlist seeds—contains ***both* 2,4-D *and* glyphosate**.

In 2015, the World Health Organization's International Agency for Research on Cancer found that **glyphosate is a probable carcinogen**, while 2,4-D is classified as a possible carcinogen.[20] No agency has yet assessed the carcinogenicity (or other potential adverse health effects) of the two active ingredients *in combination*, nor the *cumulative or synergistic effects of the two ingredients together*, or with glufosinate or with other product additives.

Yet an international team of scientists publishing this month in the peer-reviewed journal, *Carcinogenesis*, has found that chemical mixtures of non-carcinogenic chemicals *can* have cumulative effects, potentially resulting in cancer, and concluded that "we now also need to be seriously concerned about the ways in which exposures to combinations of disruptive, but otherwise non-carcinogenic, environmental agents are able to act in concert with one another to instigate the disease."[21]

Weed resistance will increase and spread

As of today, 23 species of weeds around the world have developed resistance to 2,4-D (a significant increase from the 16 resistant species identified in 2012).[22] The most recent case is the alarming and widely reported emergence of 2,4-D resistant palmer amaranth in Kansas, which follows confirmed 2,4-D resistance in waterhemp in Missouri.[23]

Furthermore, cross-resistance to 2,4-D and multiple herbicides poses an even greater challenge for farmers cultivating 2,4-D crops in the future, with some weeds already showing resistance to up to 6 modes of action. 2,4-D-resistant volunteer plants in corn and soybean fields will likely become weeds in themselves the following season, posing an additional headache for farmers trying to sow a new crop.

As Dr. David Mortensen, weed scientist at the University of Pennsylvania, has written:

> The new transgenes [in Dow's Enlist seeds and Monsanto's Xtend seeds] will allow 2,4-D and dicamba to be applied at higher rates, in new crops, in the same fields in successive years, and across dramatically expanded areas, creating intense and consistent selection pressure for the evolution of resistance. Taken together, the current number of synthetic auxin–resistant species, the broad distribution of glyphosate-resistant weeds, and the variety of pathways by which weeds can evolve multiple resistance suggest that the potential for synthetic auxin–resistant or combined synthetic auxin– and glyphosate-resistant weeds in transgenic cropping systems is actually quite high.[24]

The government of South Africa may be aware that in the U.S., over 90 million acres of farmland are currently infested with nearly impossible-to-manage glyphosate-resistant weeds. Our country's rapid and widespread adoption of RoundupReady corn, cotton and soybean drove the emergence of what many farmers now call "superweeds." Introducing 2,4-D and dicamba-resistant crops, as we have done in the U.S., will simply speed cross-resistance and mire farmers further in the increasingly ineffective trap of the herbicide treadmill.

Alternatives to herbicide-resistant GMO seeds exist

Fortunately, reliance on herbicide-resistant GMO cropping systems are not the only weed management option for South Africa, or indeed for any country. Non-chemical, low-till ecological weed management practices and ecological, biodiversified farming systems offer safe, robust, productive, profitable — and climate-resilient— approaches to farming.[25] Effective weed management practices includes cover cropping, planting living mulches and multi-year crop rotation. A growing number of farmer in the US are opting out of herbicide-intensive GMO systems and are transitioning their farms to organic and ecological farming methods.

Done well, these agroecological approaches do more than enable farmers to manage weeds effectively: they enable farmers to increase soil organic matter, conserve soil moisture, support healthy crop plants that are resistant to disease and insect pressure, provide diverse and nutrient-rich diets, protect biodiversity and providers of critical ecosystem services like pollinators, while enhancing farmers' ability to mitigate and adapt to climate change. As such, they offer a far more promising approach to farming than reliance on a highly hazardous drift-prone herbicide such as 2,4-D, to which a growing number of weeds are already resistant.

Summary

Harms to human health, increased crop damage from drift, and rapid evolution of resistant weeds are readily foreseeable consequences, should South Africa approve 2,4-D maize.

With deep respect for the South African people, and concern for the success, resilience and sustainability of South Africa's farmers and agricultural sector, we urge the South African government to reject Corteva (Dow/DuPont)'s application for approval of its 2,4-D resistant maize varieties.

Sincerely,

Marcia Ishii-Eiteman, PhD

Senior Scientist

Attached:

- Letter to US EPA from 70 Health Professionals regarding use of 2,4-D on Enlist crops (22 June 2012)
- Mortensen, D. et al. 2012. Navigating a Critical Juncture for Sustainable Weed Management. *BioScience* Vol. 62 (1): 75-84

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SUBMITTED ELECTRONICALLY

June 22, 2012

OPP Docket
Environmental Protection Agency Docket Center (EPA/DC)
Mail Code: 28221T
1200 Pennsylvania Ave. NW
Washington, DC 20460-0001

Re: 1. Docket EPA–HQ–OPP–2011–0835 (corn)

- Registration Number and File Symbol: 62719-640 and 62719-AUO: active ingredients – 2,4-D choline salt and glyphosate; proposed use – Enlist AAD-1 Corn (DAS-40278-9)
- Registration Number and File Symbol: 62719-AGO: active ingredient – 2,4-D choline salt; proposed use – Enlist AAD-1 Corn (DAS-40278-9)

2. Docket EPA–HQ–OPP–2012–0306 (soybeans)

- Registration Number and File Symbol: 62719-AUU: active ingredient – 2,4-D choline salt; proposed use – Enlist AAD-12 Soybeans (DAS-68416-4)

Dear Mr. Walsh,

We are 70 physicians, nurses, public health scientists and other health professionals who together respectfully request that EPA deny Dow AgroScience's new use applications for 2,4-D choline salt and glyphosate for use on DAS-40278-9 corn, 2,4-D choline salt for use on DAS-40278-9 corn, and 2,4-D choline salt for use on DAS-68416-4 soybeans.

Widespread planting of 2,4-D GE corn is projected to substantially increase the use of 2,4-D. Experts estimate that use of this herbicide in corn may rise from 3-4 million pounds today to over 100 million pounds over the next decade; 2,4-D soybeans and cotton would boost usage still more.[1]

Studies in humans have reported associations between exposure to 2,4-D and non-Hodgkin's lymphoma, a cancer of the lymphocytes (white blood cells).[2] This finding is consistent with other studies finding that 2,4-D increases lymphocyte replication in exposed farmworkers,[3] and that 2,4-D formulations are cytotoxic and mutagenic.[4] [5] For example, in human lymphocytes, 2,4-D causes chromosome breakage and aberrant cells.[6] In 2010, according to the National Cancer Institute, approximately 65,540 people in the United States were diagnosed with non-Hodgkin's lymphoma. The incidence of this disease in the United States has increased to about double the rate seen in the 1970s, even when adjusted for population growth and aging.[7] 2,4-D is likely to be responsible for a fraction of cases of non-Hodgkin's lymphoma each year, although it is difficult to quantify the exact numbers.

Many animal studies show that 2,4-D exhibits hormone-disrupting activity and also affects the function of the neurotransmitters, dopamine and serotonin.[8] Interference with hormones and neurotransmitters can cause serious and lasting effects during fetal and infant development, including birth defects, neurological damage and interference with reproductive function. Human studies support the results of the animal studies. Male farm sprayers exposed to 2,4-D have lower sperm counts and more spermatic abnormalities compared to men who are not exposed to this chemical. In Minnesota, higher rates of birth defects have been observed in wheat-growing areas of the state with the highest use of 2,4-D and other herbicides of the same class.[9] This increase was most pronounced among infants who were conceived in the spring, the time of greatest herbicide use. A larger study in agricultural counties in Minnesota, Montana, North Dakota and South Dakota found significant increases in malformations of the circulatory and respiratory systems, especially among infants conceived in April-June in wheat-growing counties.[10] In the same study, infant deaths from birth defects among males were significantly elevated.

2,4-D is classified by the EPA as a hazardous air pollutant and by the State of California as a toxic air contaminant. Human exposure to 2,4-D is widespread, including among children. Studies in Iowa, North Carolina and Ohio, for example, found 2,4-D in the carpet dust of 83-98 percent of homes sampled, despite the fact that most homeowners reported that they had not used the pesticide recently.[11][12] These studies imply that 2,4-D is blowing in or being tracked into homes, and many studies have shown that chemicals – including 2,4-D – in house dust end up on children's hands and in their bodies.

EPA is scheduled to begin a registration review of 2,4-D late this year or early next year, the first such review since 2,4-D was last re-registered in 2005. This review will involve consideration of the latest science on 2,4-D's toxicity, and will also give EPA the opportunity to consider Dow's applications in the context of strict new dioxin exposure standards issued by the Agency earlier this year as part of its ongoing analysis of dioxin toxicity. In light of the massive projected increases in 2,4-D use and exposure that the registrations would enable, it would be highly imprudent of EPA to take any action at this time.

For all of the above reasons, we ask EPA to deny Dow AgroScience's new use applications for 2,4-D choline salt to be used with Dow's 2,4-D resistant corn and soybeans. At the least, we urge EPA to defer any decision on Dow's application until completion of its 2,4-D registration review.

SIGNED*:

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Navigating a Critical Juncture for Sustainable Weed Management
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Navigating a Critical Juncture for Sustainable Weed Management

DAVID A. MORTENSEN, J. FRANKLIN EGAN, BRUCE D. MAXWELL, MATTHEW R. RYAN, AND RICHARD G. SMITH

Agricultural weed management has become entrenched in a single tactic—herbicide-resistant crops—and needs greater emphasis on integrated practices that are sustainable over the long term. In response to the outbreak of glyphosate-resistant weeds, the seed and agrichemical industries are developing crops that are genetically modified to have combined resistance to glyphosate and synthetic auxin herbicides. This technology will allow these herbicides to be used over vastly expanded areas and will likely create three interrelated challenges for sustainable weed management. First, crops with stacked herbicide resistance are likely to increase the severity of resistant weeds. Second, these crops will facilitate a significant increase in herbicide use, with potential negative consequences for environmental quality. Finally, the short-term fix provided by the new traits will encourage continued neglect of public research and extension in integrated weed management. Here, we discuss the risks to sustainable agriculture from the new resistant crops and present alternatives for research and policy.

Keywords: agriculture production, agroecosystems, transgenic organisms, sustainability, biotechnology

Overreliance on glyphosate herbicide in genetically modified (GM) glyphosate-resistant cropping systems has created an outbreak of glyphosate-resistant weeds (Duke and Powles 2009, NRC 2010). Over recent growing seasons, the situation became severe enough to motivate hearings in the US Congress to assess whether additional government oversight is needed to address the problem of herbicide-resistant weeds (US House Committee on Oversight and Government Reform 2010). One of our coauthors (DAM) delivered expert testimony at these hearings, in which he expressed the views described in this article. Biotechnology companies are currently promoting second-generation GM crops resistant to additional herbicides as a solution to glyphosate-resistant weed problems. We believe that this approach will create new resistant-weed challenges, will increase risks to environmental quality, and will lead to a decline in the science and practice of integrated weed management (IWM). The rapid rise in glyphosate-resistant weeds demonstrates that herbicide-resistant crop biotechnology is sustainable only as a component of broader integrated and ecologically based weed management systems. We argue that new policies are needed to promote integrated approaches and to check our commitment to an accelerating transgene-facilitated herbicide treadmill, which has significant agronomic and environmental-quality implications (figure 1).

Effective weed management is critical to maintaining agricultural productivity. By competing for light, water, and nutrients, weeds can reduce crop yield and quality and can lead to billions of dollars in global crop losses annually. Because of their ability to persist and spread through the production and dispersal of dormant seeds or vegetative propagules, weeds are virtually impossible to eliminate from any given field. The importance of weed management to successful farming systems is demonstrated by the fact that herbicides account for the large majority of pesticides used in agriculture, eclipsing inputs for all other major pest groups. To no small extent, the success and sustainability of our weed management systems shapes the success and sustainability of agriculture as a whole.

In the mid-1990s, the commercialization of GM crops resistant to the herbicide glyphosate (Monsanto's Roundup Ready crops) revolutionized agricultural weed management. Prior to this technology, weed control required a higher level of skill and knowledge. In order to control weeds without also harming their crop, farmers had to carefully select among a range of herbicide active ingredients and carefully manage the timing of herbicide application while also integrating other nonchemical control practices. Glyphosate is a highly effective broad-spectrum herbicide that is phytotoxically active on a large number of weed and crop species across a wide range of taxa (Duke and Powles 2009). Engineered to express enzymes that are insensitive to or can metabolize glyphosate, GM glyphosate-resistant crops have enabled farmers to easily apply this herbicide in soybean, corn, cotton, canola, sugar beet, and alfalfa and to control problem weeds without harming the crop (Duke and Powles 2009).

Growers were attracted to the flexibility and simplicity of the glyphosate and glyposhate-resistant crop technology package and adopted the technology at an unprecedented rate. After emerging on the market in 1996,

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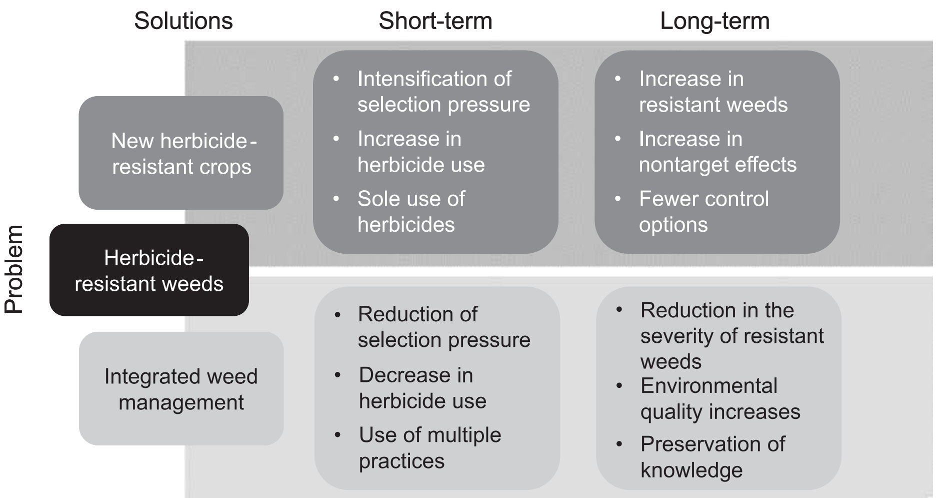

Figure 1. A conceptual model of the alternative solutions—and their potential consequences—presently available for addressing glyphosate-resistant weed problems.

glyphosate-resistant soybeans accounted for 54% of US hectares by 2000 (Duke and Powles 2009). In 2008, crops resistant to glyphosate were grown on approximately 96 million hectares (ha) of cropland internationally and account for 63%, 68%, and 92% of the US corn, cotton, and soybean hectares, respectively (Duke and Powles 2009). The technology is effective and easy to use, and farmers have often responded to these benefits by exclusively planting glyphosate-resistant cultivars and applying glyphosate herbicide in the same fields, year after year (Duke and Powles 2009, NRC 2010).

Unfortunately, this single-tactic approach to weed management has resulted in unintended—but not unexpected—problems: a dramatic rise in the number and extent of weed species resistant to glyphosate (Heap 2011) and a concomitant decline in the effectiveness of glyphosate as a weed management tool (Duke and Powles 2009, NRC 2010). As the area planted with glyphosate-resistant crops increased, the total amount of glyphosate applied kept pace, creating intense selection pressure for the evolution of resistance. This dramatic increase in glyphosate use would not have been possible without glyphosate-resistant crop biotechnology. The number and extent of weed species resistant to glyphosate has increased rapidly since 1996, with 21 species now confirmed globally (Heap 2011). Although several of these species first appeared in cropping systems where glyphosate was being used without a resistant cultivar, the most severe outbreaks have occurred in regions where glyphosate-resistant crops have facilitated the continued overuse of this herbicide. The list includes many of the most problematic agronomic weeds, such as Palmer amaranth (*Amaranthus palmeri*), horseweed (*Conyza canadensis*), and Johnsongrass (*Sorghum halepense*), several of which infest millions of hectares (Heap 2011).

The next generation of herbicide-resistant crops

To address the problem of glyphosate-resistant weeds, the seed and agrichemical industries are developing new GM cultivars of soybean, cotton, corn, and canola with resistance to additional herbicide chemistries, including dicamba (Monsanto) and 2,4-D (2,4-dichlorophenoxyacetic acid; Dow AgroSciences) (Behrens MR et al. 2007, Wright et al. 2010). Dicamba and 2,4-D are both in the synthetic auxin class of herbicides, which have been widely used for weed control in corn, cereals, and pastures for more than 40 years. These herbicides mimic the physiological effects of auxin-type plant-growth regulators and can cause abnormal growth and eventual mortality in a wide variety of broadleaf plant species. In addition to species with recently evolved resistance, several important broadleaf weed species are naturally tolerant to glyphosate but susceptible to synthetic auxins. In cropping systems where glyphosate-resistant or -tolerant weeds are major problems, dicamba and 2,4-D applications would provide an effective weedmanagement tool. Although several other transgene–herbicide combinations are currently in the research and development pipeline (Duke and Powles 2009), these modes of action already have significant resistant-weed issues or do not control weeds as effectively as dicamba or 2,4-D herbicides. Consequently, we expect that synthetic auxin–resistant cultivars will be embraced by growers and planted on rapidly increasing areas in the United States and worldwide over the next 5–10 years.

In addition to their weed management utility, there are a number of agronomic drivers that may further accelerate the adoption of the new resistant cultivars. First, soybean, cotton, and many other broadleaf crops are naturally extremely sensitive to synthetic auxin herbicides and show distinctive injury symptoms when they encounter trace doses (figure 2; Breeze and West 1987, Al-Khatib and Peterson 1999, Everitt and Keeling 2009, Sciumbato et al. 2004). Most US growers rely on commercial applicators to spray herbicides, and when susceptible and synthetic auxin–resistant fields are interspersed, there may be a high probability for application mistakes in which susceptible fields are accidentally treated with dicamba or 2,4-D. Second, synthetic auxins are extremely difficult to clean from spray equipment (Boerboom 2004), and low residual concentrations of these compounds in equipment could damage susceptible cultivars. Growers and applicators may need to have equipment dedicated to dicamba or 2,4-D to avoid damage from residual concentrations. Third, some formulated products of

Figure 2. Photo of soybean responding to a drift-level exposure to dicamba herbicide, exhibiting typical symptoms of cupped-leaf morphology and chlorotic-leaf margins. Photograph: J. Franklin Egan.

dicamba and 2,4-D have high volatility (Grover et al. 1972, Behrens R and Lueschen 1979), and the combination of particle and vapor drift may generate frequent incidents of significant injury or yield loss to susceptible crops. Moreover, the seed and chemical industries are becoming increasingly consolidated, making it more difficult for growers to find high-yielding varieties that do not also contain transgenic herbicide-resistance traits. Combined, these four agronomic drivers suggest that once an initial number of growers in a region adopts the resistant traits, the remaining growers may be compelled to follow suit in order to reduce the risk of crop injury and yield loss.

If herbicide-resistant-weed problems are addressed only with herbicides, evolution will most likely win

Glyphosate-resistant weeds rapidly evolved in response to the intense selection pressure created by the extensive and continuous use of glyphosate in resistant crops. Anticipating the obvious criticism that the new synthetic auxin–resistant cultivars will enable a similar overuse of these herbicides and a new outbreak of resistant weeds, scientists affiliated with Monsanto and Dow have argued that synthetic auxin–resistant weeds will not be a problem because (a) currently very few weed species globally have evolved synthetic auxin resistance, despite decades of use; (b) auxins play complex and essential roles in the regulation of plant development, which suggests that multiple independent mutations would be necessary to confer resistance; and (c) synthetic auxin herbicides will be used in combination or rotation with glyphosate, which will require weeds to evolve multiple resistance traits in order to survive (Behrens MR et al. 2007, Wright et al. 2010). Although these arguments have been repeated in several high-profile journals, the authors of those arguments have conspicuously left out several important facts about current patterns in the distribution and evolution of herbicide-resistant weeds.

First, similar arguments were made during the release of glyphosate-resistant crops. Various industry and university scientists contended that details of glyphosate's biochemical interactions with the plant enzyme EPSPS (5-enolpyruvylshikimate-3-phosphate synthase) combined with the apparent lack of resistant weeds after two decades of previous glyphosate use indicated that the evolution of resistant weeds was a negligible possibility (Bradshaw et al. 1997).

Second, it is not the case that "very few" weed species have evolved resistance to the synthetic auxin herbicides. Globally, there are 28 species, with 6 resistant to dicamba specifically, 16 to 2,4-D, and at least 2 resistant to both active ingredients (table 1). And although many of these species are not thought to infest large areas or cause significant economic harm, data on the extent of resistant weeds are compiled through a passive reporting system, in which area estimates are voluntarily supplied by local weed scientists after a resistant-weed problem becomes apparent. Synthetic auxin–resistant weeds may appear unproblematic because these species currently occur in cropping systems in which other herbicide modes of action are used that can effectively mask the extent of the resistant genotypes (Walsh et al. 2007). Furthermore, the claim that 2,4-D resistance is unlikely to evolve because of the complex and essential functions that auxins play in plants is unsubstantiated. In many cases in which resistance has evolved to synthetic auxins, the biochemical mechanism is unknown. However, in at least two cases, dicamba-resistant *Kochia scoparia* (Preston et al. 2009) and dicamba-resistant *Sinapis arvensis* (Zheng and Hall 2001), resistance is conferred by a single dominant allele, indicating that resistance could develop and spread quite rapidly (Jasieniuk and Maxwell 1994).

The final dimension of the industry argument is that by planting cultivars with stacked resistant traits, farmers will be able to easily use two distinct herbicide modes of action and prevent the evolution of weeds simultaneously resistant to both glyphosate and dicamba or 2,4-D. The logic behind this argument is simple. Because the probability of a mutation conferring target-site resistance to a single-herbicide mode of action is a very small number (generally estimated as one resistant mutant per 10^{-5} to 10^{-10} individuals [Jasieniuk and Maxwell 1994]), and because distinct mutations are assumed to be independent events, the probability of multiple target-site resistance to two modes of action is the product of two very small numbers (i.e., 10^{-10} to 10^{-20}). For instance, if the mutation frequency for a glyphosate-resistant allele in a weed population is 10^{-9}, and the frequency for a dicamba mutant is also 10^{-9}, the frequency of individuals simultaneously carrying both resistant alleles would be 10^{-18}. If the population density of this species is assumed to be around 100 seedlings per square meter (m^2) of cropland (10^6 per ha), it would require 10^{12} ha of cropland to find just one mutant individual with resistance to both herbicides. For point of reference, there are only about 15×10^8 ha of cropland globally. Therefore, even if the weed species were globally distributed, and all of the world's crop fields

Table 1. Global diversity and extent of the 28 weed species with resistance to synthetic auxin herbicides.

Year	Common name	Scientific name	Herbicides	Location	Acres
1952	Wild carrot	*Daucus carota*	2,4-D	Ontario	<1
1957	Spreading dayflower	*Commelina diffusa*	2,4-D	Hawaii	No data
1964	Field bindweed	*Convolvulus arvensis*	2,4-D	Kansas	No data
1975	Scentless chamomile	*Matricaria perforata*	2,4-D	France	101–500
1975	Scentless chamomile	*Matricaria perforata*	2,4-D	United Kingdom	101–500
1979	Canada thistle	*Cirsium arvense*	MCPA	Sweden	No data
1981	Musk thistle	*Carduus nutans*	2,4-D, MCPA	New Zealand	1001–10,000
1983	Gooseweed	*Sphenoclea zeylanica*	2,4-D	Philippines	1–5
1985	Canada thistle	*Cirsium arvense*	2,4-D, MCPA	Hungary	No data
1985	Common chickweed	*Stellaria media*	Mecoprop	United Kingdom	No data
1988	Yellow starthistle	*Centaurea solstitialis*	Picloram	Washington	1–5
1988	Tall buttercup	*Ranunculus acris*	MCPA	New Zealand	1001–10,000
1989	Globe Fingerrush	*Fimbristylis miliacea*	2,4-D	Malaysia	51–100
1990	Wild mustard	*Sinapis arvensis*	2,4-D, dicamba, dichloprop, MCPA, mecoprop, picloram	Manitoba	51–100
1993	Wild carrot	*Daucus carota*	2,4-D	Michigan	11–50
1993	Corn poppy	*Papaver rhoeas*	2,4-D	Spain	10,001–100,000
1994	Wild carrot	*Daucus carota*	2,4-D	Ohio	1001–10,000
1995	Kochia	*Kochia scoparia*	Dicamba	North Dakota	101–500
1995	Kochia	*Kochia scoparia*	Dicamba, fluroxypr	Montana	1001–10,000
1995	Yellow Burhead	*Limnocharis flava*	2,4-D	Indonesia	1001–10,000
1995	Gooseweed	*Sphenoclea zeylanica*	2,4-D	Malaysia	No data
1996	False cleavers	*Galium spurium*	Quinclorac	Albera	51–100
1997	Italian thistle	*Carduus pycnocephalus*	2,4-D	New Zealand	No data
1997	Kochia	*Kochia scoparia*	Dicamba	Idaho	1–5
1998	Barnyardgrass	*Echinochloa crus-galli*	Quinclorac	Louisiana	501–1,000
1998	Common hempnettle	*Galeopsis tetrahit*	Dicamba, fluroxypr, MCPA	Alberta	101–500
1998	Yellow Burhead	*Limnocharis flava*	2,4-D	Malaysia	11–50
1999	Barnyardgrass	*Echinochloa crus-galli*	Quinclorac	Brazil	1–5
1999	Barnyardgrass	*Echinochloa crus-galli*	Quinclorac	Arkansas	1–5
1999	Gulf cockspur	*Echinochloa crus-pavonis*	Quinclorac	Brazil	1–5
1999	Wild radish	*Raphanus raphanistrum*	2,4-D	Australia	10,001–100,000
1999	Carpet burweed	*Soliva sessilis*	Clopyralid, picloram, triclopyr	New Zealand	6–10
2000	Junglerice	*Echinochloa colona*	Quinclorac	Colombia	11–50
2000	Gooseweed	*Sphenoclea zeylanica*	2,4-D	Thailand	11–50
2002	Smooth crabgrass	*Digitaria ischaemum*	Quinclorac	California	11–50
2002	Marshweed	*Limnophila erecta*	2,4-D	Malaysia	501–1,000
2005	Common lambsquarters	*Chenopodium album*	Dicamba	New Zealand	11–50
2005	Indian hedge-mustard	*Sisymbrium orientale*	2,4-D, MCPA	Australia	51–100
2006	Wild radish	*Raphanus raphanistrum*	2,4-D, MCPA	Australia	1–5
2007	Prickly lettuce	*Lactuca serriola*	2,4-D, dicamba, MCPA	Washington	101–500
2008	Wild mustard	*Sinapis arvensis*	Dicamba	Turkey	101–500
2009	Barnyardgrass	*Echinochloa crus-galli*	Quinclorac	Brazil	No data

Note: Some species have evolved resistance to various synthetic auxin herbicides on multiple independent occasions in different locations. Compiled from Heap (2011).
2,4-D, 2,4-Dichlorophenoxyacetic acid; MCPA, 2-methyl-4-chlorophenoxyacetic acid.

were treated with both herbicides, it would appear virtually impossible to select a single weed seedling exhibiting multiple resistance.

The problem with this reassuring analysis is that it contradicts recent evidence. Weed species resistant to multiple herbicide modes of action are becoming more widespread and diverse (figure 3). There are currently 108 biotypes in 38 weed species across 12 families possessing simultaneous resistance to two or more modes of action, with 44% of these having appeared since 2005 (Heap 2011). Common waterhemp (*Amaranthus tuberculatus*) simultaneously resistant to glyphosate, ALS, and PPO herbicides infests 0.5 million ha of corn and soybean in Missouri (Heap 2011). Rigid ryegrass (*Lolium rigidum*) populations resistant to seven distinct modes of action infest large areas of southern Australia (Heap 2011). Weeds can defy the probabilities and evolve multiple resistance through a number of mechanisms.

First, when a herbicide with a new mode of action is introduced into a region or cropping system in which weeds resistant to an older mode of action are already widespread and problematic, the probability of selecting for multiple target-site resistance is not the product of two independent, low-probability mutations. In fact, the value is closer to the simple probability of finding a resistance mutation to the new mode of action within a population already extensively resistant to the old mode of action. For instance, in Tennessee, an estimated 0.8–2 million ha of soybean crops are infested with glyphosate-resistant horseweed (*C. canadensis*) (Heap 2011). Assuming seedling densities of 100 per m^2 or 10^6 per ha (Dauer et al. 2007) and a mutation

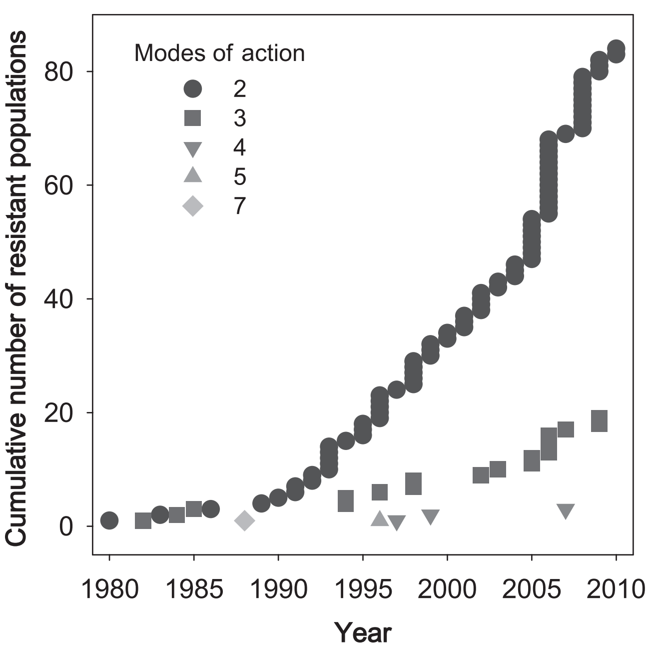

Figure 3. Global increases in the number of weed populations since 1980 across 38 species that exhibit simultaneous resistance to two or more distinct herbicide modes of action (MOA). Data compiled from Heap 2011.

frequency for synthetic auxin resistance of 10^{-9}, this implies that next spring, there will be 800–2000 horseweed seedlings in the infested area that possess combined resistance to glyphosate and a synthetic auxin herbicide ((2×10^6 ha infested with glyphosate resistance) $\times$ (10^6 seedlings per ha) $\times$ (1 synthetic auxin–resistant seedling per 10^9 seedlings) = 2000 multiple-resistant seedlings). In this example, these seedlings would be located in the very fields where farmers would most likely want to plant the new stacked glyphosate- and synthetic auxin–resistant soybean varieties (the fields where glyphosate-resistant horseweed problems are already acute). Once glyphosate and synthetic auxin herbicides have been applied to these fields and have killed the large number of susceptible genotypes, these few resistant individuals would have a strong competitive advantage and would be able to spread and multiply rapidly in the presence of the herbicide combination.

Second, several weed species have evolved cross-resistance, in which a metabolic adaptation allows them to degrade several different herbicide modes of action. Mutations to cytochrome P450 monooxygenase genes are a common mechanism for cross-resistance (Powles and Yu 2010). Plant species typically have a large number of P450 genes (e.g., the rice genome contains 458 distinct P450 genes), which are involved in a variety of metabolic functions, including the synthesis of plant hormones and the hydrolyzation or dealkylation of herbicides and other xenobiotics. Weeds with P450 mediated resistance are widespread and increasingly problematic. For instance, across Europe and Australia, numerous populations of *L. rigidum* and *Alopecurus myosuroides* occur with various combinations of P450 resistance to the ALS-, ACCase-, and photosystem II–inhibitor herbicides (Powles and Yu 2010). Given the diversity and ubiquity of P450 monoxygenases in plant genomes, it is possible that in the near future, a weed species could evolve a mutation that enables it to degrade glyphosate and the synthetic auxins.

Historically, the use of the synthetic auxin herbicides has been limited to cereals or as preplant applications in broadleaf crops. The new transgenes will allow 2,4-D and dicamba to be applied at higher rates, in new crops, in the same fields in successive years, and across dramatically expanded areas, creating intense and consistent selection pressure for the evolution of resistance. Taken together, the current number of synthetic auxin–resistant species, the broad distribution of glyphosate-resistant weeds, and the variety of pathways by which weeds can evolve multiple resistance suggest that the potential for synthetic auxin–resistant or combined synthetic auxin– and glyphosate-resistant weeds in transgenic cropping systems is actually quite high. One hundred ninety-seven weed species have evolved resistance to at least 1 of 14 known herbicide modes of action (Heap 2011), and the discovery and development of new herbicide active ingredients has slowed dramatically over recent decades. Given that herbicides are a cornerstone of modern weed management, it seems unwise to allow the new GM herbicide-resistant crops to needlessly accelerate and exacerbate resistant-weed evolution.

Increasing herbicide applications and the consequences for environmental quality

In the early promotions of their new resistant cultivars, scientists from Dow and Monsanto have been advocating herbicide programs that combine current rates of glyphosate with 225–2240 grams (g) per ha of dicamba (Arnevik 2010) or 560–2240 g per ha of 2,4-D (Olson and Peterson 2011). Therefore, the technology will not involve a substitution of herbicide active ingredients but will instead lead to additional herbicide use. If the rate of adoption of this technology follows the general trajectory of glyphosate-resistant crops, the result could be a profound increase in the total amount of herbicide applied to farmland (figure 4). This trend would move us in the opposite direction of the reduced chemical inputs that scientists in sustainable agriculture have long advocated. As the seed and agrichemical industries move closer to the commercialization of new resistant traits, it is worth pausing to ask what the environmental-quality consequences of this increase may be.

Dicamba and 2,4-D have been widely used in agriculture for over 40 years, and recent US Environmental Protection Agency (USEPA) reviews have classified both herbicides as being relatively environmentally benign (USEPA 2005, 2006). Both herbicides have low acute and chronic toxicities to mammalian, bird, and fish model organisms; degrade fairly rapidly in the soil; and are not known to bioaccumulate. Not surprisingly, however, both dicamba and 2,4-D are extremely toxic to broadleaf plants. For many terrestrial and aquatic plant species, the USEPA assessments rank the ecotoxicological risks for both dicamba and 2,4-D well above their set levels of concern (USEPA 2005, 2006). In a relative-risk assessment comparing a suite of 12 herbicides commonly used in wheat, Peterson and Hulting (2004) reported the risk to terrestrial plants for dicamba and 2,4-D as being 75 and 400 times greater than glyphosate, respectively.

All herbicides can have negative impacts on nontarget vegetation if they drift from the intended areas either as wind-dispersed particles or as vapors evaporating off of the application surface. Because of their volatility and effects at low doses, past experience with injury to susceptible crops has indicated that the synthetic auxin herbicides may be especially prone to drift problems (Behrens R and Lueschen 1979, Sciumbato et al. 2004, US House Committee on Oversight and Government Reform 2010). Research has shown that using recommended application equipment (e.g., spray nozzle types) and applying herbicides under appropriate weather conditions can reduce particle drift. Modern formulations and chemistries of synthetic auxin products also can minimize vapor drift. However, growers and commercial applicators do not always use appropriate or recommended herbicide application practices, especially if these technologies are more costly. The new resistant cultivars will enable growers to apply synthetic auxin herbicides several weeks later into the growing season, when higher temperatures may increase volatility and when more varieties of susceptible crops and nontarget vegetation are leafed out, further increasing the potential for nontarget drift damage.

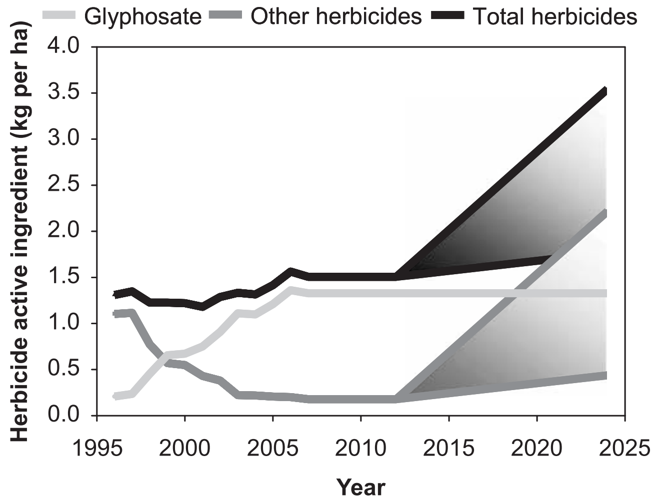

Figure 4. Total herbicide active ingredient applied to soybean in the United States. The data from 1996 to 2007 are adapted from Figure 2-1 in NRC (2010), and the projected data are based on herbicide programs described by Arnevik (2010) and Olson and Peterson (2011). To forecast herbicide rates from 2008 to 2013 we assumed that the applications of glyphosate and other herbicides will remain constant at 2007 levels until 2013, when new resistant soybean varieties are likely to become available. We estimated yearly increases in synthetic auxin herbicides (assumed to drive increases in other herbicides) by assuming that the adoption of stacked synthetic auxin–resistant cultivars mirrors the adoption of glyphosate-resistant cultivars, such that 91% of soybean hectares are resistant to synthetic auxin herbicides within 12 years. We further assumed that all soybean hectares with stacked resistance to glyphosate and synthetic auxin herbicides will receive an annual application of glyphosate and dicamba or 2,4-D. We assumed that the use rates of glyphosate will remain at current levels, and our estimates for dicamba and 2,4-D encompass lower (0.28 kilograms [kg] per hectare [ha]) and higher (2.24 kg per ha) use rates, which are in line with the rates currently used on tolerant crops (i.e., corn and wheat) and with rates being researched and promoted by Dow and Monsanto.

Plant diversity plays fundamental roles in agroecosystem sustainability, and major increases in dicamba and 2,4-D use may negatively affect multiple aspects of this important resource. First, as was discussed above, herbicide drift or misapplications could create a strong incentive for growers to plant resistant seeds as insurance against crop damage from herbicide drift or applicator mistakes, even if they are not interested in applying synthetic auxin herbicides themselves. This effect could further augment the portion of the seed market and of the landscape garnered by the resistant seed varieties, which would reduce genotypic diversity and restrict farmers' access to different crop varieties. Second, a large number of agronomic, fruit, and vegetable crops are susceptible to injury and yield loss from drift-level exposures to these herbicides (figure 2; Breeze and West 1987, Al-Khatib and Peterson 1999, Everitt and Keeling 2009). In the past, growers have reported issues with injury from drift and have recently voiced concerns about the expanded use of the synthetic auxin herbicides (Behrens R and Lueschen 1979, Boerboom 2004, Sciumbato et al. 2004, US House Committee on Oversight and Government Reform 2010). Landscapes dominated by synthetic auxin–resistant crops may make it challenging to cultivate tomatoes, grapes, potatoes, and other horticultural crops without the threat of yield loss from drift. Finally, a growing body of research has demonstrated that wild plant diversity in uncultivated, seminatural habitat fragments interspersed among crop fields helps support ecosystem services valuable to agriculture, including pollination and biocontrol (Isaacs et al. 2009). More research is needed in order to understand the impact that increased synthetic auxin applications may have on the quality and function of these plant diversity resources.

IWM: An alternative path forward

Glyphosate-resistant weeds—and herbicide-resistant weeds in general—represent a significant challenge to our food system. However, simply inserting additional resistant traits into crops and promoting the continuous application of glyphosate and dicamba or 2,4-D is by no means the only available or practical solution to this problem (figure 1). Growers and scientists have been working together for decades to develop a robust set of management practices that could be implemented to address resistant-weed issues.

Integrated weed management is characterized by reliance on multiple weed management approaches that are firmly underpinned by ecological principles (Liebman et al. 2001). As its name implies, IWM integrates tactics, such as crop rotation, cover crops, competitive crop cultivars, the judicious use of tillage, and targeted herbicide application, to reduce weed populations and selection pressures that drive the evolution of resistant weeds. Under an IWM approach, a grain farmer, instead of relying exclusively on glyphosate year after year, might use mechanical practices such as rotary hoeing and interrow cultivation, along with banded pre- and postemergence herbicide applications in a soybean crop one year, which would then be rotated to a different crop, integrating different weed management approaches. In fact, long-term cropping-system experiments in the United States have demonstrated that cropping systems that employ an IWM approach can produce competitive yields and realize profit margins that are comparable to, if not greater than, those of systems that rely chiefly on herbicides (Pimentel et al. 2005, Liebman et al. 2008, Anderson 2009). In one study, herbicide inputs were reduced by up to 94%, and profit margins were comparable to those of a conventional system (Liebman et al. 2008).

The introduction of glyphosate-resistant crops was a key factor enabling no-till crop production, which increased from 45 million to 111 million ha worldwide between 1999 and 2009 (Derpsch et al. 2010). Although no-till production can provide soil-quality and conservation benefits, it is dependent on herbicides, and the overreliance on glyphosate now threatens its sustainability. Effective IWM typically involves some tillage, such as interrow cultivation over a multiyear crop rotation. Despite a common misconception that tillage is always destructive to soil, a growing body of cropping systems research has demonstrated that where limited tillage is balanced in an IWM context with soil-building practices such as cover-cropping or manure applications, high levels of soil quality can be maintained. For example, rotational-tillage systems have recently been reported to accumulate and store more soil organic matter than no-till systems (Venterea et al. 2006). Greater soil carbon and nitrogen were observed in integrated systems that used tillage, cover crops, and manure than in a conventionally managed no-till system, regardless of whether cover crops were used in the no-till system (Teasdale et al. 2007). These results illustrate that soil-quality benefits associated with no-till systems can also be achieved using IWM that includes limited tillage.

Recent research has also demonstrated that IWM strategies are effective in managing herbicide-resistant weeds. For example, glyphosate-resistant horseweed in no-till soybean can be controlled by integrating cover crops and soil-applied residual herbicides (Davis VM et al. 2009). In a recent experiment in which the integration of tillage and cover crops was evaluated for controlling glyphosate-resistant Palmer amaranth in Georgia, the combination of tillage and rye cover crops reduced Palmer amaranth emergence by 75% (Culpepper et al. 2011). In addition to cultivation and cover crops, other practices can be used to manage resistant-weed populations. Researchers in Australia suggested two cultural weed management practices for reducing glyphosate-resistant weed populations: increasing a crop's competitive ability through higher seeding rates and preventing seed rain of resistant weeds by collecting or destroying weed seed at harvest (Walsh and Powles 2007). Area-wide management plans in which farmers cooperate to limit the hectares over which a single herbicide is applied can prevent the spread of a resistant species across a landscape (Dauer et al. 2009).

Unfortunately, the knowledge infrastructure needed to practice IWM in the future may be atrophying. Although seed and chemical companies can generate enormous revenues through the packaged sales of herbicides and transgenic seeds, the IWM approaches outlined above are based on knowledge-intensive practices, not on salable products, and lack a powerful market mechanism to push them along. For instance, delaying the planting date one or two weeks until after a flush of summer annual weeds have germinated can facilitate the control of these weeds with burndown herbicides and eliminate the need for postemergence herbicide applications. To apply this IWM practice, a farmer would need detailed, region-specific information on crop and weed ecology in order to choose the planting date that optimizes a tradeoff between better weed control and a shorter growing season (Nord et al. 2011). Because the use of this practice might reduce the need for herbicide inputs, modern seed-chemical firms would have little incentive to pursue the required research or to extend the knowledge to growers. IWM knowledge serves as a public good, and it requires locally adapted and ongoing public research, combined with effective extension education programs, in order to address current and future weed management challenges.

In his congressional testimony, Troy Roush (Indiana farmer and vice president of the American Corn Grower's Association) remarked that farmers are "working on the advice largely of industry anymore.… Public research is dead; it's decimated" (US House Committee on Oversight and Government Reform 2010). Indeed, several trends indicate that the public support needed for IWM research and extension is declining. First, the formula funds in the US Farm Bill that have historically provided support for land-grant universities to pursue farming systems research tailored to their growing regions have been steadily phased out in favor of competitive grant programs, in which the research topics and agendas are set by federal funding agencies (Huffman et al. 2006, Schimmelpfennig and Heisey 2009). The total amount of federal public funding for agriculture has basically remained flat since 1980, whereas private research investments have steadily increased (Schimmelpfennig and Heisey 2009). During this period, partnerships between land-grant universities and chemical and biotechnology companies have increased in number and extent (Schimmelpfennig and Heisey 2009), and in several respects, research activities in public colleges of agriculture have transitioned to parallel the activities and priorities of the biotechnology industry (Welsh and Glenna 2006). A recent survey of the membership of the Weed Science Society of America suggests that these patterns are influencing the research priorities of scientists who specialize in weed management (Davis AS et al. 2009). As of 2007, 41% of the membership reported topics related to herbicide efficacy as their primary research focus, whereas only 22% reported focusing on topics with a broader integrated perspective.

When the next major weed management challenge arrives, will we be prepared with the knowledge and skilled workforce capable of implementing an integrated solution?

Policies to cultivate IWM

Several changes in policy could reduce the likelihood that the next generation of herbicide-resistant crops will result in negative consequences for food production and the environment and could ensure that IWM thrives as a sustainable alternative in the future. To be clear, we are not advocating the prohibition of herbicide-resistant crops; there is ample evidence attesting to the economic and environmental benefits that can be realized if these technologies are used judiciously (Duke and Powles 2009). Rather, we are advocating that concrete policy steps be taken to ensure that we learn from our problematic experiences with glyphosate resistance, such that the new herbicide-resistant crops are adopted as only one component of fully integrated weed management systems. Such policies could include USEPA-mandated resistant-weed management plans, fees discouraging single-tactic weed management, improved grower education programs implemented through industry–university–government collaborations, and environmental payments that connect IWM to broader environmental goals.

First, the USEPA, and similar agencies in other countries, should require that registration of new transgene–herbicide crop combinations explicitly address herbicide-resistant-weed management. Weed scientists and industry spokespeople have frequently expressed skepticism that resistance management regulations would be enforceable and have instead placed the burden on education and promotional efforts by agribusinesses or the responsible behavior of individual growers (NRC 2010). However, in *Bacillus thuringiensis* (Bt) cropping systems, regulations requiring non-Bt refugia have largely prevented the evolution of insect resistance to Bt and protected the effective and sustainable use of this biotechnology (NRC 2010), although improvements may be needed in monitoring and compliance (NRC 2010). For herbicides, regulations need not be focused on local refugia but could implement spatially explicit, area-wide management plans that work to reduce selection pressure at landscape or regional scales. These plans could mandate carefully defined patterns of herbicide rotation or could set upper limits on the total sales of a specific herbicide active ingredient or of a resistant seed variety within an agricultural county. Efficient allocation of crop hectares treated with a specific herbicide or planted with a resistant variety could be achieved through a tradable-permit system.

Second, fees directly connected to the sale of herbicide-resistant seeds or the associated herbicides could provide a disincentive for overreliance on the technology package (Liebman et al. 2001). These fees could be scaled to specifically discourage overuse, such that a grower or applicator would be charged only if a specified threshold in planted hectares or successive applications were exceeded. The proceeds from the fees could be funneled directly into funds for public university research and education programs that promote the understanding and adoption of IWM techniques among farmers. In Iowa, similar levies on pesticides are used to fund Iowa State University's Leopold Center, which has played a significant role in the development of IWM science (Liebman et al. 2001).

Third, stronger partnerships among industry, universities, and government could foster IWM through more effective education and extension efforts. When new herbicide active ingredients or herbicide-resistant crop varieties are brought to market, seed and agrichemical companies often develop product-stewardship plans intended to educate growers, applicators, and salespeople on IWM practices to prevent or manage herbicide-resistant weeds. However, because past and current stewardship plans have been developed by an industry driven by herbicide sales, the IWM concept articulated in these plans is largely reduced to simply rotating or combining herbicide active ingredients and fails to promote a more comprehensive set of chemical and nonchemical weed management practices. The ever-growing number of herbicide-resistant weeds (figure 3; Heap 2011) indicates that a solely industry-led approach to herbicide stewardship and IWM education is insufficient and ineffective. Before synthetic auxin–resistance traits are brought to market, stewardship plans could be revised with more comprehensive participation and oversight from government and universities. For instance, sales literature and labels for resistant crops and the associated herbicides could include more extensive detail on a wider set of resistance-management practices available to growers and could provide access to university or government IWM information resources. Industry-sponsored field days and promotional events could be required to include university scientists and to provide ample time devoted to IWM education. Renewal of herbicide or GM trait registrations could be made contingent on compliance with these more aggressive stewardship plans.

Finally, as research continues to develop and refine IWM practices, their adoption could be enhanced through environmental-support payments that connect weed management to broader environmental issues. This approach is working in Maryland, where, following growing public concern and awareness of declining water quality and hypoxic "dead zones" from nutrient loading caused by agriculture, the Maryland Department of Agriculture launched a cost-sharing program that provided growers in the Chesapeake Bay watershed with economic incentives to grow winter cover crops (MDA 2011). Cover crops can reduce nutrient losses from fields (Munawar et al. 1990), and by creating weed-suppressive mulches, they can also be a valuable component of IWM systems. This program has been widely embraced by farmers and contributed to cover crops' being planted on hundreds of thousands of hectares, which has had a positive impact on water quality and promoting IWM techniques. This effort is supported by state and federal tax dollars and has been sustained because citizens living within the watershed were provided with information regarding the impact that agricultural practices have on water quality, resulting in a willingness to pay for mitigation efforts, including cover crop cost-sharing programs. The foundation of successful IWM is diversity, which is also a well-recognized pillar of sustainable agroecosystem management. Similar opportunities may exist to connect IWM practices to a range of environmental goals, including on-farm energy efficiency, soil-quality management, or agrobiodiversity conservation, and may help advance toward a more multifunctional agriculture (Boody et al. 2005). Research and extension programs exploring these connections would need to be scaled up if sufficient willingness to pay for alternatives can be achieved.

No single policy will adequately address our growing overreliance on a transgenic approach to weed management. Rather, a combination of policies will be necessary to secure a more sustainable agriculture, including (a) regulatory mandates for resistant-weed management, (b) enhanced funding for IWM research and education, (c) collaboratively designed herbicide stewardship plans, and (d) environmental payment incentives for the adoption of IWM practices. Next-generation GM herbicide-resistant crops are rapidly moving toward commercialization. Given this critical juncture, it is time to consider the implications of accelerating the transgene-facilitated herbicide treadmill and to rejuvenate our commitment to alternative policies that safeguard agriculture and the environment for the long term.

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