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Resistance Management and Sustainable Use of Agricultural Biotechnology

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While crop biotechnologies deployed worldwide with herbicide-resistant (HR) or insect-resistant (IR) traits have provided significant economic and environmental benefits, these benefits are threatened by the evolution of insect and weed resistance. This article examines why field-level resistance has not posed a problem for IR crops but has become a growing problem for HR crops. Key factors include compatibility of the technologies with integrated pest and weed management and the regulatory and institutional setting in which they were deployed. Transgenic crops will be more sustainably deployed if they are embedded in integrated pest and weed management with strong, outward extension linkages to farmers and backward linkages to research institutions. Public and private plant breeding can play a critical role in developing stacked traits that reduce overreliance on single chemical compounds or toxins. Extension can serve two important functions along with its traditional role of information provision: (a) facilitating farmer collective action for area-wide resistance management and (b) providing government agencies with information needed to increase the flexibility and cost-effectiveness of resistance management regulations. The article concludes by discussing some implications for resistance management in developing countries.

Key words: resistance, herbicides, IPM, weed management, Bt cotton.

Introduction

Genetically modified (GM) crops first became commercially available in 1996. In countries where they have been approved, growers have rapidly adopted GM crops with herbicide resistant (HR), insect resistant (IR), or both traits. Where approved, GM varieties accounted for 90% of soybean, 78% of cotton, 72% of canola, and 60% of maize hectares by 2008 (Table 1). Among HR crops, the dominant trait is resistance to the herbicide glyphosate.

Adoption of IR and HR crops has generated significant economic benefits. For IR crops, this has come from higher yields due to greater insect control, reduced insecticide costs, or both (Brookes & Barfoot, 2008; Carpenter, Gianessi, Sankula, & Silvers, 2002; Gianessi, Silvers, Sankula, Carpenter, 2002; Marra, 2001; Marra, Pardey, & Alston, 2002; National Research Council [NRC], 2010; Price, Lin, Falck-Zepeda, Fernandez-Cornejo, 2003; Qaim, 2009). Evidence of farm profit gains from HR crops has been more mixed (Bonny, 2007; Lin, Price, & Fernandez-Cornejo, 2001; Marra et al., 2002; Webster, Bryant, & Earnest, 1999). Other studies have considered hard-to-measure benefits of HR crops, such as simplicity, convenience, flexibility, safety (to crops, workers, or the environment), scope for saving management time, and compatibility with conservation tillage (Alston, Hyde, Marra, & Mitchell, 2002; Bonny, 2007; Brookes & Barfoot, 2008; Carpenter & Gianessi, 1999; Fernandez-Cornejo, Hendricks, & Mishra, 2005; Gardner, Nehring, Nelson, 2009; Gianessi, 2008; Hurley, Mitchell, Frisvold, 2009a; Marra, Piggott, & Carlson, 2004; Piggott & Marra, 2008; Sydorovych & Marra, 2007, 2008).

GM crops also provide environmental benefits. Adoption of IR Bt cotton has led to shifts to insecticides with lower toxicity and less harmful environmental effects (Kleter et al., 2007; Knox, Constable, Pyke, Gupta, 2006; NRC, 2010; Wossink & Denaux, 2006). Adoption of Bt maize has had a more limited impact on insecticide use (Qaim, 2009). This is because its main target pest, European corn borer, is not effectively controlled with insecticides. Thus, the main benefits to maize growers are yield gains rather than reduced insecticide applications.

Similar results have been reported for HR crops resistant to the herbicide glyphosate, which often substitutes for herbicides with higher toxicity and persistence in the environment (Brimner, Gallivan, & Stephenson, 2004; Fernandez-Cornejo, Klotz-Ingram, & Jans, 2002; Gardner & Nelson, 2008; Nelson & Bullock, 2003). Adoption of HR crops appears to encourage conserva-

Table 1. Adoption of GM crop varieties (as a share of world hectares and as a share of hectares in approving countries).

	Cotton	Maize	Canola	Soybeans
Total world hectares planted to GM varieties (%)	49%	23%	27%	66%
Hectares planted to GM varieties in countries where GM varieties of crop have been approved (%)	78%	60%	72%	90%
Hectares in countries where GM varieties of crop have been approved (% of total)	63%	39%	37%	74%
Hectares in countries where GM varieties of crop have *not* been approved (% of total)	37%	61%	63%	26%

Source: Author's calculation from James (2009) and FAOSTATS (UN, FAO).

tion tillage (Carpenter et al., 2002; Fawcett & Towery, 2002; Fernandez-Cornejo & Caswell, 2006; Frisvold, Boor, & Reeves, 2009a; Kalaitzandonakes & Suntornpithug, 2003; Kim & Quinby, 2003; Marra et al., 2004; Roberts, English, Gao, Larson, 2006; Trigo & Cap, 2003). This can reduce soil erosion and attendant water pollution (Brookes & Barfoot, 2008; NRC, 2010).

There are concerns, however, that the economic and environmental benefits of GM crops may not be sustainable because of the evolution of insect and weed resistance (e.g., Benbrook, 2001; Lemaux, 2008). Entomologists have documented three cases of field-evolved resistance to Bt crops. Field-evolved resistance is a genetically based decrease in susceptibility of an insect population to a toxin caused by that population's exposure to the toxin in the field (Tabashnik, Van Rensburg, & Carrière, 2009). This is contrast to cases where laboratory insect strains become resistant after exposure to the toxin within the laboratory. These are (a) *Spodoptera frugiperda* (J. E. Smith; fall armyworm) resistance to Cry1F toxin in Bt corn in Puerto Rico; (b) *Busseola fusca* (Fuller; maize stalk borer) resistance to Cry1Ab in Bt corn in South Africa; and (c) *Helicoverpa zea* (Boddie; cotton bollworm) resistance to Cry1Ac and Cry2Ab in Bt cotton in the US Southeast (Matten, Head, & Quemada, 2008; Tabashnik, Gassmann, Crowder, Carrière, 2008; Tabashnik et al., 2009; Van Rensburg, 2007). Despite these three cases of resistance to Bt crops, there have yet to be economically significant field-control problems.

Tabashnik et al. (2009) completed a comprehensive analysis of resistance monitoring data from 41 studies across five continents for Bt cotton and maize. In addition to the three noted cases of resistance, they reported on five studies from China and India with ambiguous evidence of resistance of *Helicoverpa armigera* to Cry1Ac in Bt cotton. For seven target pests, however, they reported strong evidence of no increase in the frequency of resistance to Bt toxins in GM crops. They also reported sustained susceptibility of some populations of *H. zea* and *H. armigera*.

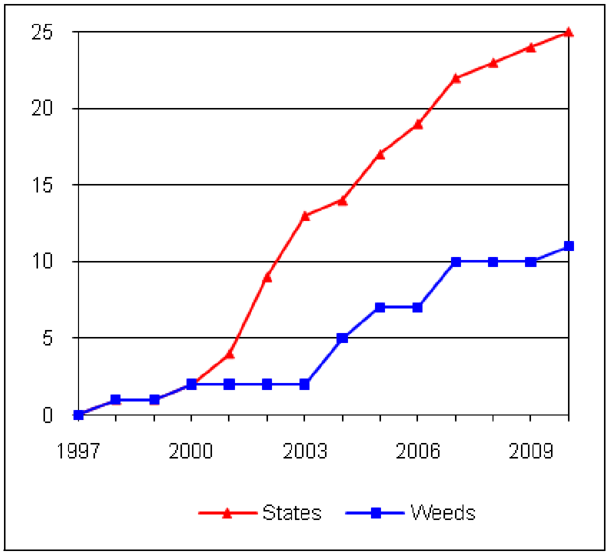

Figure 1. Number of weed species with glyphosate-resistant populations (blue) and number of states with glyphosate-resistant weed populations (red).

Source: Heap (2011)

To date, weed resistance to herbicides that complement HR crops has been a more significant problem than insect resistance to Bt crops. Prior to 1998, there were no reported glyphosate-resistant weed species in the United States. By 2010, however, glyphosate resistance had been confirmed for 11 species in the United States (Figure 1) and 21 species worldwide (Heap, 2011). US resistant weed species are spread across 19 states (Figure 1). Costs of HR weeds can be significant, ranging from $5-130/hectare (Mueller, Mitchell, Young, Culpepper, 2005; Scott & VanGessel, 2007; Webster & Sosnoskie, 2010). In severe cases, growers may opt to abandon fields altogether (Culpepper, Whitaker, MacRae, & York, 2008). In the United States, glyphosate resistant weeds have proven problematic in selected areas and to varying degrees for cotton, soybeans, peanuts in rotation with cotton, maize (Culpepper et al., 2006, 2008; Davis, Kruger, Young, & Johnson, 2010; Foresman & Glasgow, 2008; Steckel, Main, Ellis, & Mueller, 2008; VanGessel, 2001; Webster & Sosnoskie, 2010), and even perennial crops in California (Hanson, Shrestha, & Shaner, 2009).

Evolution of resistance to Bt crops and to herbicides that complement HR crops poses three risks. First, it would deprive agricultural producers of pecuniary and non-pecuniary benefits of these crops. Second, it would deprive society of environmental benefits of reduced chemical applications, movements toward less toxic and persistent chemicals, and conservation tillage. Third, it may have a powerful, negative demonstration effect on countries considering approval of GM varieties for the first time. Despite their apparent benefits, many countries remain reluctant to approve GM crop varieties. Countries that have not approved GM crops with HR or IR traits account for 37% of cotton, 61% of maize, 63% of canola, and 26% of soybean hectares worldwide (Table 1).

Aims and Scope

This article reviews the features and performance of resistance management strategies for IR and HR transgenic crops. It attempts to explain why resistance problems have developed for HR crops but not for Bt crops. One key factor has to do with fundamental attributes of the two technologies and their compatibility with integrated pest and weed management. Another key factor was the regulatory setting where each type of technology was deployed. While resistance management for Bt crops was federally mandated with their initial introduction, resistance management practices for HR crops have been voluntary and decentralized. Regulatory requirements for managing resistance to Bt crops also spurred greater levels of research into the science of pest resistance. Consequently, scientific understanding of resistance management strategies for Bt crops is relatively advanced.

Next, this article draws policy lessons from the US experience. First, GM IR and HR crops will be more sustainable if they are embedded in integrated pest and weed management programs with strong, outward extension linkages to farmers and backward linkages to research institutions. Second, public and private plant breeding plays a critical role in resistance management by developing varieties with traits that reduce over-reliance on any single toxin or chemical compound. Examples include pyramiding of Bt traits or development of crops resistant to multiple herbicides, encouraging rotation of compounds with different modes of action. Third, developing varieties with stacked or pyramided traits will be more effective if implemented as a complement to, rather than a substitute for, active grower participation in integrated pest management (IPM) and integrated weed management (IWM) programs. Fourth, extension can serve two important functions along with its traditional role of information provision. Extension can facilitate farmer collective action for area-wide resistance management. It can also provide government agencies with information needed to increase the flexibility and cost-effectiveness of resistance management regulations. The article concludes by discussing implications for resistance management for GM crops in developing countries.

Resistance Management: A Tale of Two Technologies

HR weeds have begun to pose economically important problems for use of GM HR crops, while insect pest resistance has yet to pose similar problems for Bt crops. Resistance management has been affected by differences in (a) the basic features of these technologies, (b) how they have been integrated into production systems, and (c) how they have been regulated. Understanding how these differences contribute to the success or failure of resistance management will be crucial for developing effective resistance management policies in the future.

Narrow-spectrum vs. Broad-spectrum Control

Bt stands for *Bacillus thuringiensis*, a soil bacterium. Bt, distributed worldwide, is found in agricultural and forest soils, savannas, and deserts, as well as on leaf surfaces of temperate-zone trees. Bt is commonly found in natural soils and in sericulture farms, insect-rearing facilities, flourmills, grain storage facilities, and other environments where insects are found (Lambert & Peferoen, 1992). The Bt toxin has a narrow spectrum of toxicity to a limited number of lepidopteran and coleopteran pests. The Bt cells produce crystal-like proteins that disrupt midgut membranes, killing particular insects that ingest them. Normally the proteins are not active against humans, other vertebrates, and most beneficial insects (Mendelsohn, Kough, Vaituzis, & Matthews, 2003; Naranjo, Ruberson, Sharma, Wilson & Wu, 2008). Foliar spray applications of Bt are one of the most important insecticides used in US certified organic crop production (Hutcheson, 2003; Walker, Mendelsohn, Matten, & Alphin, 2003; Walz, 1999). Under US federal standards, crops using low-toxicity insecticides—such as neem, pyrethrum, sabadilla, insecticidal soaps, and Bt sprays—can be certified as organic.

Because Bt cotton works continually, Cannon (2000) raised concerns that it might discourage insect scouting and monitoring, which are key elements of IPM. But, the shift to narrow-spectrum control meant that cotton growers had to consider pest population dynamics *more*—not less—carefully. Rather than spraying broad-spectrum insecticides and counting on collateral control of other insects, cotton growers now had to monitor non-target pests more closely for supplemental control. Bt cotton also appears to exhibit little activity against natural cotton predators and non-target species, especially compared to cotton sprayed with insecticides (Head et al., 2005; Naranjo, 2005; Naranjo et al., 2008; Torres & Ruberson, 2005). Reducing impacts on natural predators is another key element of an IPM strategy.

While there is no single definition of IPM—Bajwa and Kogan's (2004) compendium lists 67 definitions—an over-arching theme is the substitution of knowledge for insecticides. IPM requires an understanding of factors influencing pest populations, such as pest predators, host plant resistance, and choice and timing of cultural practices. This, in turn requires integration of agronomy, plant genetics, economics, pest population dynamics, and ecology.

Fitt (2008) notes a challenge of producing Bt crops is that they are "living crops" with greater abundance of beneficial insects and secondary pests. While the first-generation, single-Bt toxin varieties were highly effective against tobacco budworm (*Heliothis virescens*) and pink bollworm (*Pectinophora gossypiella*), they were less effective against cotton bollworm (*H. zea*). Growers often continued to use sprays to control *H. zea*. In addition, there has been some increase in secondary pest activity as growers reduced broad-spectrum sprays for pests that Bt controls. Results from Australia and the United States suggest that despite secondary pests, Bt cotton adoption has led to a reduction in total insecticide applications (Fitt, 2008; Frisvold, 2009; Frisvold & Pochat, 2004). Reductions in sprays for Bt's target pests have outweighed increases in sprays to non-target pests. Studies have found similar results in parts of China (e.g., Huang et al., 2002; Lu et al., 2010; Wang et al., 2009). Secondary pest outbreaks have posed more serious problems elsewhere in China (e.g., Wang, Just, & Pinstrup-Andersen, 2006), in India, and in South Africa (Fitt, 2008; Lemaux, 2008; Naranjo et al., 2008). Lu et al. (2010) found that, although Bt cotton reduced total pesticide use on cotton fields, secondary mirid outbreaks infested fields of other crops.

The performance of Bt crops may have more to do with the technical and institutional capacity of regions where they are deployed than with the technology itself (Fitt, 2008). Moving from broad-spectrum sprays to a diversity of narrow-spectrum control targeting different pests requires greater knowledge of entire pest complexes. Successful deployment of Bt technology requires complementary provision of education and training about these complexes. The sustainable use of Bt crops is a management-intensive endeavor. However, its narrow spectrum makes it compatible with many aspects of IPM—protection of natural predators and beneficial insects, reduced use of chemical insecticides, matching specific treatments to specific pests, and avoiding over-reliance on any one compound to control multiple pests. These features of IPM, in turn, are critical for delaying resistance (Bates, Zhao, Roush, & Shelton, 2005; Ellsworth & Martinez-Carillo, 2001).

In contrast to Bt crops, HR crops are resistant to broad-spectrum, non-selective herbicides such as glyphosate and glufosinate. While Bt crops complement management-intensive IPM strategies, a benefit of HR crops is their ability to simplify decisions and reduce management time (Bonny, 2007; Gianessi, 2008). Glyphosate controls more than 300 weed species (Green, Hazel, Forney, & Pugh, 2008). Growers can control many broadleaf and grass weeds effectively using one herbicide instead of many different ones (Fernandez-Cornejo & McBride, 2002). Adoption of HR crops appears positively associated with off-farm work of farm households and appears to be household labor saving (Fernandez-Cornejo et al., 2005, 2007; Gardner et al., 2009). In addition, HR crops increase flexibility by expanding the window when growers can apply herbicides (Bonny, 2007). This reduces sensitivity to weather and timing of operations. This makes HR crops highly complementary with part-time farming. There is evidence that small-scale, part-time farm operations are less likely to be aware of resistance problems or to adopt resistance management practices (Johnson & Gibson, 2006; Johnson et al., 2009).

A crucial part of delaying the evolution of weed resistance is diversifying control strategies (Duke & Powles, 2009). This can be achieved by using combinations of chemical (herbicides) and non-chemical (e.g., tillage, row spacing, crop rotations) tactics (Beckie, 2006; Beckie & Gill, 2006). Within chemical control, it is also important to avoid over-reliance on herbicides with the same site of action (Beckie, 2006; Beckie & Gill, 2006; Green, 2007; Green et al., 2008).

Adoption of HR crops in the United States has contributed to movements away from resistance management practices. Since the introduction of glyphosate-resistant crops, glyphosate applications have risen substantially at the expense of other compounds (Bonny, 2007; Fernandez-Cornejo & McBride, 2002; Kim & Quinby, 2003). Rapid adoption of HR crops has led to vast areas of the American South relying heavily on glyphosate in extensive monoculture. Beckie (2006, pp. 809) argues that this has encouraged "simplified cropping systems favoring a few dominant weed species and frequent use of single site-of-action herbicides." Complementary adoption of reduced- and no-till practices has reduced the diversity of weed-control measures and increased reliance on single-site compounds. While crop rotations may break weed cycles and reduce reliance on the same compounds, continued use of HR varieties of different crops can subvert the effectiveness of crop rotations as a resistance management strategy. In a survey of more than 1,200 growers, Hurley et al. (2009b) reported that about two-thirds of corn and cotton growers and nearly half of soybean growers planned to rotate their current HR crop with another HR crop. Rotating the use of herbicides with different modes of action or using herbicide mixtures are other strategies to delay resistance (Beckie & Reboud, 2009; Green, 2007). These too appear to have declined. In a survey of agricultural professionals and growers, Harrington et al. (2009) found that 54% of respondents reported a decrease in rotation between herbicides with different sites of action, while 46% reported a decrease in use of crop rotations. (Interestingly, survey responses suggest that adoption of IR crops has <u>not</u> led to movements away from IPM practices). Among corn, cotton, and soybean producers, Frisvold, Hurley, and Mitchell (2009b) found a significant negative association between planting of glyphosate-resistant crops and use of herbicides with different modes of action. While Bt crops have proven compatible with IPM practices that delay resistance, adoption of HR crops has encouraged behavior that has increased selection pressure.

Regulatory Environment

Another critical difference between Bt and HR crops was that resistance management was federally regulated and mandatory for Bt crops, but not for HR crops. Why the difference? One reason was the value of microbial Bt sprays in organic agriculture. Organic grower groups became concerned that widespread use of the Bt toxin on vast acres of field crops would hasten resistance to Bt. In response to this concern, the Environmental Protection Agency (EPA) found that preventing Bt resistance was in the "public good" and that steps to prevent resistance should be established (Walker et al., 2003). Because the Bt toxin was embodied in the crop itself, Bt crops were regulated as pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Environmental and organic groups were unhappy with the EPA's initial registration of Bt crops in the mid-1990s. They petitioned (in 1997) then filed suit (in 1998) against the EPA to block Bt crop deployment (Fox, 2000; Vogt & Parish, 2001). While these groups withdrew their suit in 2000, they continued critiques of EPA biotechnology regulation throughout the re-registration process for these crops.

The EPA requires integrated resistance management (IRM) for Bt corn and Bt cotton (US EPA, 2001). IRM strategies have been developed in consultation with EPA and USDA staff, universities, public interest groups, grower groups, and Monsanto (the first developer of Bt cotton; Matten & Reynolds, 2003). The EPA regularly convenes Scientific Advisory Panels (SAPs) to review underlying science and evidence regarding pest resistance and to revise IRM regulations (US EPA, 2001, 2006a, 2006b). For IRM, the EPA requires (a) mandatory refuge requirements, (b) resistance monitoring, (c) remedial action plans to address resistance problems, (d) IRM compliance monitoring, (e) grower education, (f) grower agreements, and (g) annual reports.

Requiring resistance management plans for Bt crops was unprecedented in pesticide regulation. Resistance management plans have not been required for conventional pesticides (Matten et al., 2008). To delay resistance, the EPA requires growers who plant Bt cotton to also plant non-Bt cotton on a minimum percentage of their total cotton acreage. Similar rules apply for planting of Bt and non-Bt corn. These non-Bt "refuge" acres allow susceptible pests to survive and mate with adults resistant to the Bt toxin, delaying the development of resistance in the pest population. Results from entomological studies suggest refuges can significantly delay the onset of resistance (Carrière & Tabashnik, 2001; Gould, 1998; Heckel, Gahan, Gould, Daly, Trowell, 1997; Tabashnik et al., 2003).

The EPA used its authority under FIFRA to require science-based development of specific resistance management regulations. The EPA relied on recommendations from the National Academy of Sciences and from the SAPs it convened to spur further research on resistance management (NRC, 2000; US EPA, 2001). This led to significant advances in Bt resistance modeling and empirical analysis. This greatly increased the knowledge base concerning how and how well the refuge strategy might work. Results in the field have been consistent with entomologists' theoretical predictions (Tabashnik et al., 2009).

The EPA registered Bt crops at roughly five-year intervals and required extensive information on resistance management science and compliance as a condition of re-registration (Mendelsohn et al., 2003). This maintained pressure on Monsanto and on growers to demonstrate compliance with the refuge strategy. For growers, the threat of EPA cancellation may have felt more real than the risk of Bt resistance. The environmental economics literature suggests that voluntary adoption of environmental practices is more likely if there is an underlying threat of regulation (Alberini & Segerson, 2002; Khanna & Damon, 1999; Lyon & Maxwell, 2002; Ribaudo, 1998).

One may think of the susceptibility of weeds or insects to pesticides as common-pool resources (Miranowski & Carlson, 1986). Current use of a chemical will deplete the susceptibility of pests over time. While it is in the long-term collective interest of growers to maintain this susceptibility by adopting resistance management practices, such adoption is individually costly. Individual growers have an incentive to deplete susceptibility (while counting on others <u>not</u> to). Refuge requirements are a government mechanism to prevent such free riding for the growers' collective benefit. In a survey of corn growers, Alexander (2007) found that among Bt corn adopters, 75% agreed that refuges would maintain the technology's effectiveness, 68% agreed refuges benefited all growers, and less than 19% agreed that the benefits of refuges were not worth the time and effort. However, only 40% of growers agreed that they would plant a refuge if not required. This suggests the challenges of resistance management through voluntary behavior.

While resistance management practices for Bt crops are federally mandated, management of weed resistance for HR crops has been decentralized and voluntary. Bt crops have pesticidal substances incorporated into them and are thus regulated under FIFRA. HR crops do not include pesticidal compounds themselves, however, so the EPA has no clear authority to regulate HR crop varieties directly (Horne, 1992). In principle, the EPA could exert influence over weed resistance management in two areas. First, under FIFRA, the EPA has authority to regulate uses of herbicides that complement HR crops. Second, the EPA could require resistance management procedures to be implemented as a condition of granting Section 18 exemptions. The Emergency Exemption Program mandated by Section 18 of FIFRA gives the EPA authority to authorize emergency, non-registered uses of pesticides. States often make requests for Section 18 exemptions in response to pest or weed resistance that reduces the usefulness of registered compounds.

Even if the EPA decided they had authority to regulate weed resistance management, the rationale and scope for such intervention is less clear than in the case of Bt crops. Because microbial Bt sprays have been valuable for insect control in specialty crop and organic farming, there was greater scope for external costs. The loss of pest susceptibility to Bt sprays would hurt organic and specialty crop growers, but these costs would be external to Bt crop seed sellers and corn and cotton growers.

Miranowski and Carlson's (1986) seminal work on the economics of resistance management for chemical pesticides is useful for understanding why different resistance management regimes arose for HR and Bt crops. If pests are highly mobile, then management of resistance can suffer from common pool externalities. Individual farmers would have an individual incentive to deplete the common pool of pest susceptibility. Individual incentives to delay resistance may not coincide with long-term benefits of growers collectively. If pests are not especially mobile, however, resistance management is an intertemporal management problem. Growers must still weigh short-run costs of resistance management against long-term costs of resistance. However, without pest mobility, there are no externalities. Resistance management is a matter of private incentives. Without mobility, the role of government in resistance management is confined to extension and education to improve grower awareness of intertemporal tradeoffs. With highly mobile pests, however, there are social benefits to encouraging growers to manage pest resistance cooperatively for their long-term, collective benefit. Direct government regulation of resistance management as it is applied to Bt crops may be warranted.

Grower cooperation can also be achieved through methods falling short of direct government regulation. As with pest eradication programs, growers could vote to collectively implement practices. For example, for US pest-eradication programs, growers impose assessments on themselves to fund activities, restrict certain behaviors, and mandate others (such as requiring after-season plowing to prevent pest over-wintering). The role of government here is indirect—enforcing growers' collective decisions.

Miranowski and Carlson (1986) also considered the role of the supplier of the pest-control technology. If the supplier had monopoly control of the product and it

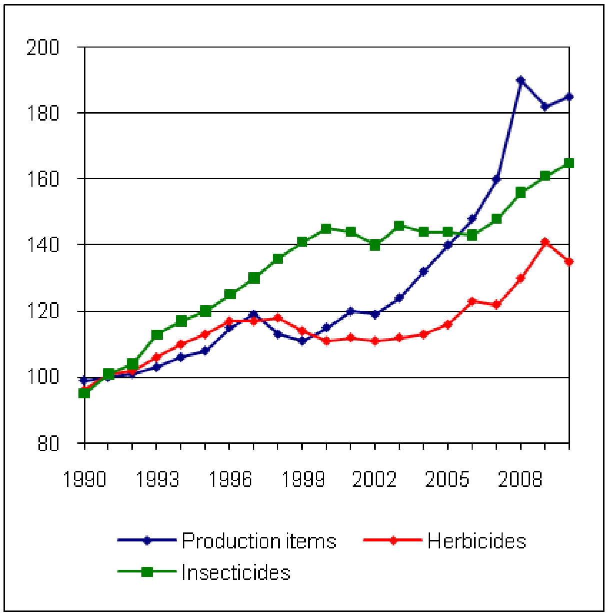

Figure 2. Indexes of prices paid by US agricultural producers for herbicides, insecticides, and all production items (1990-1992=100).

Source: US Department of Agriculture, National Agricultural Statistical Service

were sufficiently valuable, the supplier would have an incentive to manage pest susceptibility to the product as an exhaustible resource. A monopolist would have greater incentive to delay resistance than if the product were sold in a competitive market. In the case of Bt crops, the insect pests they target are highly mobile (generating one type of externality), while resistance could also harm growers relying on microbial Bt sprays (a second externality). Although Monsanto held the patent on the initial transgenic Bt crop varieties, patent length is limited and new competitors have entered the market with other Bt varieties. In contrast, weeds have generally been considered highly immobile, and glyphosate sales remain a large source of income for Monsanto.

Finally, Miranowski and Carlson (1986) considered the role of price signals in farmer decisions to manage resistance. If new pest-control products are being developed and commercialized regularly, farmers will have little incentive to manage resistance to existing products. From the early 1960s to early 1980s, prices of pesticides rose more slowly than other agricultural inputs. They argued this signaled to growers that resistance was not making effective pesticides scarce. This picture has continued for herbicides and less so for insecticides since 1990 (Figure 2). The mid 1990s saw dramatic episodes of insect resistance to pyrethroids, along with more rapid increases in conventional insecticide prices. Thus, Bt crops were introduced at a time with price signals suggesting limits to alternative insect control. In contrast, for herbicides, prices have tended to rise less rapidly than for other production inputs. Prices of glyphosate had risen relative to other herbicide and production prices in 2008 and 2009, but fell sharply in 2010. This latest price reduction is the result of patent expiration for glyphosate and a large influx of imports of generic glyphosate, produced in China. Thus, price signals for glyphosate have encouraged a “no resistance management” approach to herbicides. In contrast, because of the unique features of Bt sprays and Bt incorporated in plants, it has been more widely felt that there are no close substitutes for Bt.

Hence, resistance management for glyphosate-resistant crops has taken the form Miranowski and Carlson’s (1986) framework predicted. Actual resistance management has been left to individual growers, while the product supplier has coordinated with grower associations and extension to educate growers about resistance and its management. Herbicide price signals have not as yet signaled scarcity of effective weed-control products. While Monsanto’s loss of glyphosate market share is a disincentive to manage resistance as aggressively, glyphosate still accounts for a large share of the company’s sales revenues and profits.

Externalities in weed resistance management may be greater than previously believed, however. Mobility of resistant weed seeds may be greater than previously believed (Llewellyn & Pannell, 2009; Marsh, Llewellyn, & Powles, 2006). In California, glyphosate-resistant horseweed (*Conyza canadensis*) appears to be highly mobile (Hanson et al., 2009). Resistance to glyphosate has evolved in Palmer amaranth (*A. palmeri*) in glyphosate-resistant cotton fields throughout the Southeast United States (Culpepper et al., 2006, 2008; Culpepper, York, & Marshall, 2009; Nichols et al., 2008; Norsworthy, Griffith, Scott, Smith, & Oliver, 2008; Steckel et al., 2008; York, Whitaker, Culpepper, & Main, 2007). Regarding glyphosate-resistant Palmer amaranth, one extension publication warns that “there are no economical programs to manage this pest in cotton” (Culpepper & Kichler, 2009, p. 1). By 2008, glyphosate-resistant Palmer amaranth infested more than 240,000 hectares of land in Georgia, North Carolina, and South Carolina (Culpepper et al., 2009). An additional 87,000 hectares of cotton were infested in Arkansas (Doherty, Smith, Bullington, & Meier, 2008). HR Palmer amaranth now appears to be quite mobile.

Weed seeds are also transported via custom harvest and other custom machinery operations. Custom operators currently lack incentives to internalize external costs of spreading resistant seed. Moreover, HR crop varieties complement conservation tillage, a practice with many external benefits, which include reduced soil erosion and water sedimentation, reduced fossil fuel use for plowing, increased biodiversity, and soil carbon sequestration. If resistance management leads to significant movements away from conservation tillage (as it has in some parts of the Southeast United States), external benefits of conservation tillage would be lost. Glyphosate-resistant weeds could also lead to reversion to herbicides with more negative environmental impacts. Thus, external costs of weed resistance may be greater than previously appreciated (Marsh et al., 2006).

Even if HR weeds are more mobile and generate greater externalities than previously thought, a regulatory response would be difficult to implement. First, for weed resistance management, it is less clear what would constitute "compliance" with resistance management. For Bt crops, one can assess whether refuges are of the appropriate configuration, size, and proximity to Bt fields. There are additional restrictions on which insecticides can be sprayed on refuges, but growers and pest-control advisors are familiar with crop and purpose restrictions on insecticide applications. Some studies have examined the extent to which growers have complied with refuge requirements (Carrière et al., 2005; Goldberger, Merrill, Hurley, 2005).

In contrast, for HR crops, there are multiple crop, planting, herbicide, tillage, and machinery-cleaning choices one could make to delay resistance. How then does one measure adoption? Some studies have developed indexes characterizing the intensity of IWM adoption based on the number of practices adopted (Frisvold et al., 2009b; Hammond, Luschei, Boerboom, Nowak, 2006; Hollingsworth & Coli, 2001; Llewellyn, Lindner, Pannell, & Powles, 2007). These, however, do not address directly whether growers are adopting the most important practices.

One reviewer has suggested the possibility of mandatory reporting requirements for herbicide use, linking payment of farm program subsidies to compliance with herbicide rotation regulations. US farm legislation does make receipt of farm programs contingent on compliance with certain soil erosion and wetland protection regulations. At present, however, there are no such "compliance" provisions, making farm payments conditional on resistance management. Further, federal reporting requirements for herbicide use are limited, with only a few states mandating detailed documentation of pesticide use. In contrast to this suggested regulatory approach, Monsanto has begun offering price rebates to growers purchasing residual herbicides to be used in conjunction with glyphosate. These subsidies apply to herbicides with modes of action that differ from glyphosate and even apply to some herbicides sold by competing companies (Volkmann, 2010).

Short-run Costs of Resistance Management

Costs of adopting resistance management practices may also have been lower for Bt than for HR crops. In 1999, 40% of US cotton growers using Bt cotton planted *more* non-Bt cotton than the minimum required under regulations (Frisvold & Reeves, 2008). A detailed survey of Arizona cotton growers (Carrière et al., 2005) also found evidence of over-compliance with embedded and in-field refuge size requirements among some growers. Embedded refuges are blocks of non-Bt cotton at least 50 meters wide, planted within fields of Bt cotton. EPA regulations require the refuge area to be at least 5% of the total cotton area. In Arizona, embedded refuge size was 35% in 2002 and 2003—seven times the minimum requirement. For in-field refuges, growers must plant at least one row of non-Bt cotton for every 6-10 rows of Bt cotton (a minimum 10% refuge requirement). Average in-field refuge size was 28% in 2002 and 25% in 2003, more than double the minimum requirement. Frisvold and Reeves (2008) offer two explanations for over-compliance. First, risk aversion can explain partial adoption of technologies (Just & Zilberman, 1983). For risk-averse growers, the refuge size that maximizes expected utility may be greater than the minimum requirement.

Second, halo effects and area-wide suppression of pest populations allow some growers to reduce their Bt crop acreage and still maintain effective pest control (Alstad & Andow, 1996; Carrière et al., 2003; Frisvold & Reeves, 2008; Hutchison et al., 2010). Bt seeds sell at a price premium. Halo effects suggest that growers can reduce seed costs by planting more acreage to non-Bt varieties, without sacrificing much pest control. Frisvold and Reeves (2008) report that in areas with high adoption rates of Bt cotton, opportunity costs of refuges may be less than Bt technology fees. For some growers, refuge compliance costs are relatively small.

Turning to HR crops, in a study of adoption of 10 resistance management practices among US corn, cotton, and soybean farmers, Frisvold et al. (2009b) found infrequent adoption of three practices: supplemental tillage, cleaning equipment, and using multiple herbicides with different modes of action. Hurley et al. (2009b) found that cleaning equipment was associated with higher weed-management costs among soybean growers, supplemental tillage increased costs among corn growers, and using herbicides with different modes of action increased costs for cotton and soybean growers. Many of the practices used to delay resistance are the same as those to manage weeds after resistance has evolved (Beckie, 2006; Green et al., 2008). Some studies suggest that growers may delay adoption of IWM practices until after resistance is present (Beckie & Gill, 2006; Llewellyn et al., 2004).

The ease, flexibility, and management time-saving aspects of HR crops make them attractive to part-time farmers, or farmers for which agricultural income is a small share of total household income. This, however, can present a problem for resistance management. Part-time farmers have a smaller economic stake in preserving the efficacy of HR crops. For example, 26% of US grain and oilseed farms and 12% of cotton farmers had less than $25,000 in *gross* sales. These farms would have substantially less *net income* from agriculture. It is an open empirical question of (a) whether small-scale operations are a source of resistant weeds, and (b) if so, whether they would adopt more management-intensive IWM practices needed to control resistance. Frisvold et al. (2009b) found no strong evidence of scale effects in adoption of weed resistance management practices. However, their survey data did not include smaller farm-size classes.

Plant Breeders to the Rescue?

There is still scope to delay resistance to Bt and HR crops via plant breeding by pyramiding and stacking traits in individual crop varieties. I follow the convention of using the term “pyramiding” for combining multiple genes that confer the same trait to a crop (Ferré, Van Rie, & Macintosh, 2008; Tabashnik et al., 2009). An example is Bollgard® II cotton, which includes two Bt toxins—Cry1Ac and Cry2Ab. Stacking refers to using different genes to confer multiple traits. For example, stacked varieties might have both insect pest and herbicide resistance or might be resistant to herbicides with different modes of action. So, a Bt crop with a HR trait would be considered stacked as would a crop that possessed resistance to entirely different herbicides, while a variety using two Cry Bt toxins would have pyramided traits.

In the United States, registered Bt crops use different combinations of 11 Bt toxins (Tabashnik et al., 2009). To be successful, pyramiding requires low initial resistance to each toxin individually in a pest population. While the effectiveness against *H. zea* of the first, commercially used, single Bt toxin Cry1Ac deployed in Bt cotton was limited, a second toxin, Cry2Ab, achieves a high level of control. Resistance may still develop quickly if single-toxin and two-toxin Bt varieties are grown at the same time and in the same areas. In the United States, substantial cotton acreage with the single Cry1Ac toxin (Bollgard) has been planted in the same areas as cotton varieties with both the Cry1Ac and Cry2Ab toxins (Bollgard II). This practice was continued until 2010. In Australia, however, single-toxin Bt cotton was completely replaced by two-toxin varieties in 2004/2005 (Downes, Parker, & Mahon, 2009). Some *H. zea* populations in the southeastern United States already show field-evolved resistance to Cry1AC or to Cry2Ab (Ali & Luttrell, 2007; Ali, Luttrell, & Abel, 2007; Tabashnik et al., 2009). In Australia, *H. armigera* (a similar pest to *H. zea*) has not had field-level resistance to either Cry1Ac or to Cry2Ab. Tabashnik et al. (2009) argue that this conforms to theoretical predictions because Australia had larger refuge requirements for Bt cotton than the United States did, while in Australia single and double Bt cotton varieties were not planted at the same time. Resistance of *H. zea* to Bt toxins has not yet led to significant field-level control failures because one of the toxins is still effective, and conventional insecticides still control the pest.

Weed resistance may be delayed by developing crop varieties resistant to multiple herbicides (Green et al., 2008). Resistance can be delayed by rotating between herbicides with different modes of action and by using herbicide mixtures (reducing selection pressure on any one compound; Beckie, 2006). If a particular weed is resistant to one type of herbicide, it may still be killed by another herbicide that relies on a different mode of action. Companies are developing new crop varieties that combine glyphosate resistance with resistance to herbicides with different modes of action (Green et al., 2008). One example will be varieties that stack glyphosate resistance with resistance to different acetolactate synthase (ALS)-inhibiting herbicides. These stacked varieties will be combined with homogeneous blends (herbicide mixtures with different modes of action). Because these blends will be mixtures of currently registered herbicides, they may receive regulatory approval relatively quickly.

Combining herbicide mixtures with multiple resistant crop varieties can reduce overreliance on any single mode of action. This strategy also avoids the high cost and lengthy delays in developing novel herbicides. It raises certain questions, however. First, how many different modes of action need to be combined in one HR crop variety to delay resistance substantially? How is the potential for delay affected by the fact that some weeds are resistant to the herbicides that are to be combined. For example, some weeds are already resistant to glyphosate, others are resistant to ALS inhibitors, and some are resistant to both (e.g., Legleiter & Bradley, 2008).

Top-down vs. Bottom-up Resistance Management

Stacked or pyramided crop varieties will be a critical part of resistance management. However, this represents a rather top-down approach. Successful resistance management will likely require more than growers passively selecting market products (seed varieties and chemicals). It remains to be seen whether cross-resistance develops between different Bt toxins or whether rotation between a limited set of herbicides will be sufficient to delay resistance.

A bottom-up approach to resistance management relies on multiple strategies to control insects and weeds that include non-chemical control and is usually information-intensive. Extension can play a critical role in bottom-up resistance management strategies. First, it can provide basic information about the nature of intertemporal tradeoffs and common pool resource problems of susceptible pests.

The history of cooperative extension in Arizona is a good example of effective extension intervention to further area-wide IPM (Frisvold, 2009). In Arizona and Southern California, an extensive area-wide IPM program was already in place before the introduction of Bt cotton. This program included reliance on insect scouting, narrow-spectrum insecticides, non-chemical control, and sterile moths. It also included extension programs in pest complexes and active resistance monitoring. Introduced into this mature IPM system, Bt cotton has performed extremely well. The main target pest—pink bollworm—has shown no sign of resistance evolving.

A Bt Cotton Working Group was established in Arizona and it instituted intensive farmer education programs emphasizing the common pool resource problem of Bt resistance. The working group included participants from grower groups, seed distributors, and cooperative extension. It facilitated detailed geo-coded monitoring of refuge requirement compliance, developed remedial action plans, and has even recommended more stringent location requirements for refuges to the EPA. The call for stricter regulation from a grower group seems curious at first. However, through extension and education efforts, growers appreciated the value of taking steps to delay resistance. Second, because the recommendations came from “the bottom up,” growers had time to adjust voluntarily before the regulations became binding. Third, the working group’s science-based recommendations also included calls for regulatory flexibility in other areas that benefited growers (such as variances for seed production and approval to implement more types of refuges). The EPA has been willing to increase the flexibility of regulations if it is scientifically defensible. The ability to apply different refuge options substantially reduced the short-run costs of refuges (Frisvold & Reeves, 2008).

Bt cotton in the US Southwest is an example of a Bt crop embedded in an IPM system with strong, outward extension linkages to farmers and backward linkages to research institutions. The area has seen no decline in the susceptibility of pink bollworm to Bt cotton and total insecticide use on cotton has declined (Frisvold, 2009). Bt cotton has become the centerpiece of an area-wide program in the US Southwest (and northwest Mexico) to eradicate pink bollworm from the region. Pink bollworm populations have been reduced to such a degree that a program with a target of 100% Bt cotton planting, along with release of sterile moths, is hoped to achieve regional eradication.

Arizona’s experience highlights the value of grower collective action in resistance management. Producer groups have financed data collection and resistance management education programs. They have made data available for both research and regulatory decisions. Extension education has not been unidirectional from the university to growers. Growers have educated scientists and regulators about Bt cotton performance in the field. Grower groups have been instrumental in funding and self-enforcement of area-wide IPM practices (such as plow-down requirements and short-season cotton production). The role of growers in providing data, funding, and self-regulation provides a lesson to scientists and regulators. With advances in geographic information systems and grower assistance, one may collect detailed, spatial data on adoption of biotechnology, chemical use, yields, and compliance with refuge requirements, as well as pest and beneficial insect populations (Carrière et al., 2005; Cattaneo et al., 2006). However, if grower-supplied data is only used to ratchet up regulation, it will be less forthcoming (Frisvold, 2000). For growers, a lesson is that providing scientific data to regulators can be a means of supporting appeals for flexible, less costly regulations.

Lessons for Developing Countries

Experience from the US Southwest demonstrates that Bt crops, and especially Bt cotton, can (a) be highly compatible with IPM, (b) lead to substantial reductions in insecticides sprays for target pests, (c) lead to reductions in sprays for all pests, (d) reduce yield losses and variability, and (e) be deployed extensively over large areas for several years without the evolution of resistance. However, significant investments in IPM institutional capacity were made well before the arrival of Bt cotton. Regulatory agencies also had significant scientific capacity to formulate resistance management policies. Furthermore, grower groups were actively engaged in cooperative resistance management and area-wide pest control prior to Bt cotton introduction. There was also a constant two-way flow of data and scientific information between growers, university specialists, and the EPA. Bt and HR crops have been deployed in many developing countries with far less institutional capacity or active grower engagement in “bottom-up” cooperative resistance management.

The performance of transgenic crops will depend on the institutional and environmental setting where they are deployed as much as properties of the technologies themselves (Fitt, 2008; Kuosmanen, Pemsl, & Wesseler, 2006; Pemsl, Gutierrez, Waibel, 2008; Pemsl & Waibel, 2007). Resistance management is information-intensive and requires cooperative behavior. A “loading dock” approach of simply making new varieties available and letting growers passively select between a narrow range of products is unlikely to succeed at maintaining the effectiveness of Bt or HR crops. Growers with prior IPM training have been better able to achieve benefits from transgenic crops (e.g., Yang et al., 2005). Problems with secondary pests of Bt crops have been more pronounced where growers had less understanding of pest population dynamics (Fitt, 2008; Lemaux, 2008; Lu et al., 2010; Wang et al., 2006). Grower awareness and understanding of the process of resistance also is associated with greater compliance with resistance management policies (Goldberger et al., 2005; Kruger, Van Rensburg, & Van den Berg, 2009). Grower awareness of the importance of resistance management has been low among smallholders in South Africa (Bennett, Buthelezi, Ismael, & Morse, 2003; Kruger et al., 2009). In the Vaalharts region of South Africa, rates of compliance with refuge requirements have been low. This has contributed to rapid evolution of resistance of maize stalk borer to Bt corn (Kruger et al., 2009).

Transgenic crops have been adopted rapidly even before comprehensive IPM or IWM strategies have been established. This rapid adoption has provided economic and environment benefits over the short-to-medium term. Some of these benefits are likely to be irreversible. Examples of irreversible benefits include (a) reduced pesticide poisonings from adoption of Bt cotton in China (Hossain, Pray, Lu, Huang, Fan, & Hu, 2004; Huang et al., 2002); (b) reduced production of mycotoxins (toxic and carcinogenic chemicals produced by fungi) in Bt maize; and (c) reduced accumulation of sediments in water bodies from combined adoption of HR crops and conservation tillage (Fawcett & Towery, 2002). Invoking the Santaniello Theorem (Wesseler, 2009), such irreversible benefits provide some rationale for rapid deployment of transgenic crops.

However, sustaining benefits of agricultural biotechnology over the long term will require resistance management. Strategies to manage resistance are part of what is referred to as IPM or IWM. By whatever name used, a key concept in resistance management is the use of diverse strategies for insect and weed control. These include (a) using knowledge of biological systems and chemical modes of action, (b) using both non-chemical and chemical control, and (c) avoiding over reliance on any single toxin to achieve control (Duke & Powles, 2009; Ellsworth & Martinez-Carrillo, 2001).

Deploying transgenics in concert with IPM and IWM will be challenging in developing countries. As a reviewer noted, bringing IPM and IWM programs to farmers in developing countries will require intensive farmer training. Financial and institutional constraints often prevent such training from reaching subsistence farmers. Space does not allow a full discussion of constraints to IPM implementation in developing countries. For some recent discussions of these constraints see van Huis (2009) and Shepard et al. (2009). Managing resistance to Bt crops will require attention to the role of saved seed in developing countries. While saved seed may enhance subsistence farmer self-sufficiency, it may also thwart high-dose, refuge strategies (Showalter, Heuberger, Tabashnik, & Carrière, 2009). Despite advantages of certified seed, their cost can be a real constraint to subsistence farmers (Rodenburg & Demont, 2009). Thus, in addition to training-intensive resistance management programs, developing countries may require development of seed certification programs, improved input marketing channels, and provision of micro-credit for sustainable deployment of biotechnology (Rodenburg & Demont, 2009). This implies an active role for both government entities and public-private partnerships.

Conclusions

While IR Bt crops and HR crops can provide significant economic and environmental benefits, these benefits are threatened by the evolution of insect and weed resistance. Failure to develop successful resistance management strategies will not only deprive current adopters of the benefits of crop biotechnology, it will also have a powerful negative demonstration effect on regions yet to approve biotechnology. Field-level resistance has been scientifically documented in at least three cases for Bt crops.[1] This has not led to economically important field-level pest-control failures, either because the Bt crop variety was withdrawn from the market, because chemical control of the resistant pest remains effective, or because alternative Bt toxins remain effective. For HR crops, resistance problems are a reality in the southeastern United States. Adoption of HR crops in the United States has been rapid, in part, because HR crops made weed control less management-intensive. Effective resistance management, however, is fundamentally knowledge- and management-intensive.

Public and private plant breeding can play a critical role in delaying resistance by developing pyramided and stacked traits that reduce overreliance on single chemical compounds. However, this second generation of crop varieties still relies on a relatively narrow set of traits. Moreover, some insects and weeds have already developed resistance to individual traits that are being combined. It remains to be seen whether simply adding this small number of new traits will significantly forestall resistance evolution.

IR and HR crops will be more sustainably deployed if they are embedded in integrated pest management and integrated weed management with strong, outward extension linkages to farmers and backward linkages to research institutions. While extension plays an obvious role in disseminating information, it can also serve two other important functions. First, it can facilitate farmer collective action for area-wide resistance management. Second, it can provide government agencies with the information needed to increase the flexibility and cost-effectiveness of resistance management regulations. A lesson for developing countries is that resistance will be less likely to evolve if IR and HR crops are deployed in combination with active IPM and IWM programs. Delivering such programs to smallholders in developing countries may be especially challenging. IR and HR crops have thus far generated significant short-run economic and environmental benefits. Successful, complementary IPM and IWM programs can help sustain these benefits of agricultural biotechnologies for many years to come.

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[1] *In addition to three confirmed cases of resistance in transgenic Bt crops, there are recent reports of pink bollworm resistance to Bt cotton in India (Bagla, 2010; Tabashnik & Carrière, 2010).*

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