Insect Resistance Management for GE Crops: Industry Principles, Policies, and Programs

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Introduction

Resistance is a natural phenomenon, a result of evolution and adaptation to environment. When a pest population is exposed to a pest management tool, whether chemical, biological, or cultural, the individuals in that population that are genetically predisposed to overcome the management tool are more likely to survive and pass their genes on to the next generation. Over multiple generations, the genotypic make-up of the targeted pest population shifts from susceptibility to resistance. Insect resistance management (IRM) is the set of practices that are intended to slow this evolutionary process, delay the onset of resistance, and reduce its economic and environmental impact.

In the context of agricultural biotechnology, the rate at which resistance develops in target pest populations is influenced by genetic, biological, and operational processes (Bates et al., 2005; Gould, 1998). For genetically engineered (GE) insect protection traits, operational factors include the level of mortality the GE crops cause to the pest populations, the extent to which the GE traits are adopted across the agricultural landscapes and over time, and the diversity of other crop and non-crop hosts of the target pests in the landscapes (Gustafson et al., 2006). Biological factors include the intensity of selection pressure for resistance imposed by a crop as a result of the expression of an insecticidal trait; the extent to which the insect pests use alternative host plants; the dispersal, mating, and oviposition behavior of the insects; and fitness costs associated with resistance mechanisms (Caprio, 2001). Population genetics are driven by the genetic diversity of a pest population, including the number of genes involved in resistance to an insect protection trait; the frequency of alleles that confer resistance; the level of the resistance that is achieved; and the level of resistance conferred on heterozygous insects that carry one copy of a resistance allele and one of the wild-type susceptible allele. The most widely advocated IRM techniques involve the use of refuges, or areas of a focal crop without insect protection traits, where susceptible insects can survive; the use of “high-dose” traits that cause high levels of mortality of both susceptible insects and heterozygous insects; and combining multiple modes of action in single plants (known as “pyramiding” toxins) so that insects that are resistant (or heterozygous for resistance) to one mode of action are killed at a high rate by one or more additional modes of action (Caprio, 1998; Roush, 1998; Tang et al., 2001; Zhao et al., 2003).

Developers of GE traits are able to influence certain elements of the evolutionary process of adaptation that leads to resistance. On the biological side, developers can select insecticidal traits to which target pests are highly sensitive and target expression levels and patterns (across tissues and across crop phenology) to achieve the desired “high dose” (Bernardi et al., 2012). Developers can also combine multiple modes of action in individual plants to create pyramids that are very effective at delaying resistance (Storer et al., 2012). On the operations side, developers can provide growers with information and education on the appropriate use of traits within their farming operations and on best management practices for reducing pest populations (MacIntosh, 2010). Where refuges are important, developers can instruct growers on their necessary size and placement, ensure growers are able to buy refuge seed, and even incentivize the purchase, planting, and management of refuges so that they produce both yield and susceptible target insects (MacIntosh, 2010).

However, there are limits to the extent to which technology developers can control the evolutionary process of resistance. The range of known different insecticidal proteins that are suitable for expression in plants is currently rather narrow, with a strong reliance on Cry and Vip proteins from *Bacillus thuringiensis* (*Bt*) (Bates et al., 2005). Different target pest species have different levels of sensitivity to the available insect protection traits, and thus expression levels that meet the high-dose criterion for one pest may not meet that criterion for other pests (Buntin, 2008; Crespo et al., 2009; O’Rourke et al., 2010; Wu et al., 2007). Some important target pests, such as *Helicoverpa* spp. (corn earworms, bollworms) and *Diabrotica* spp (corn rootworms), appear to not be highly sensitive to any of the characterized proteins, being able to some extent to overcome environmental stressors that include pesticidal traits (Burkness et al., 2010; Hibbard et al., 2010, 2011; Huang et al., 2011; Storer et al., 2006). Furthermore, genetic diversity within insect species and background natural mutations mean that alleles conferring resistance or reduced tolerance are expected to be present in a target pest population even before exposure to a given plant-produced insect protection trait (Burd et al., 2003; Downes et al., 2009; Gould et al., 1997; Siegfried et al., 2014). There are also limitations on a technology provider’s ability to enforce IRM practices on the part of farmers, who can choose among different seed suppliers and technology developers.

From a farmer’s perspective, resistance management must compete for time and attention with other priorities, particularly the need to deliver high-yielding crops, making efficient use of land, fertilizers, water, pesticides, and other agricultural inputs. Refuges are by definition lower yielding than fields containing GE insect protection traits, because to be functional they must be fed on by susceptible insects. Refuges and best management practices also add to the complexity of raising crops and managing farms, requiring growers to handle different fields or different parts of fields in different ways.

Industry Commitment to Durable GE Crop Technology Deployment

The developers of insect-protected GE crops recognize that the development of resistance to their products can threaten their business success as well as that of their customers. They also recognize that, in the face of these challenges around implementation of refuge-based IRM, durable deployment of these crops requires cooperation among developers. Cross-licensing arrangements and similarities among the products available to growers means that resistance to one product can cause resistance to others, while resistance reduces the diversity of effective modes of action and increases the selection pressure for resistance to the others. Accordingly, in 2014, the member companies of CropLife International, the global federation representing the plant science industry that includes BASF, Bayer CropScience, Dow AgroSciences, DuPont Pioneer, Monsanto, and Syngenta, agreed together to a foundational set of durability commitments. These commitments recognize that (1) resistance management is fundamental to stewardship of the technology; (2) practices that promote resistance management should be embedded throughout organizations, including in R&D, regulatory, and commercial operations; and (3) the marketplace should not undermine technology sustainability.

To ensure that these commitments are carried out into practice, the industry further developed a new resistance management program through Excellence through Stewardship (ETS; see www.excellencethroughstewardship.com). ETS promotes the universal adoption of stewardship programs and quality management systems for the full life cycles of plant products. Adding IRM programs to the existing scope of ETS ensures transparency and collaboration in efforts to meet the industry commitments to technology durability. The ETS program requires that science-based, practical, IRM plans be in place for all insect protection traits, that there be industry-wide alignment on local IRM strategies, that appropriate refuge seed be available and distributed to growers, that grower IRM adoption programs be in place, and that monitoring be in place for the effectiveness of these programs, with mitigation measures should resistance develop. ETS achieves adherence to these programs through regular audits of member companies' programs and processes. The IRM component was added to ETS at the start of 2015, and the multinational companies that commercialize insect protection traits are committed to successfully completing audits by the end of 2016.

The ETS audits will cover a member company's management accountability for IRM, and strategies, processes, and programs that address regulatory requirements, market deployment, sales and customer IRM awareness, grower implementation of IRM requirements, resistance monitoring, and responses to reports of potential or actual resistance. ETS auditors will examine company records and documentation of these processes, ensuring improved transparency and accountability across the technology developers.

Non-Industry Stakeholder Engagement

It is clear that the challenges around implementing IRM at the grower level require not only dedication by the technology developers but also the direct involvement of other stakeholders that have an interest in sustainability of biotechnology in agriculture (Frisvold & Reeves, 2010). Regulatory authorities and other government agencies can promote IRM for beneficial products that increase farmer productivity and reduce the environmental footprint of agriculture. Regulatory agencies, such as the US Environmental Protection Agency and the Canadian Food Inspection Agency, that require developers to implement refuge compliance programs have proven to be effective in raising IRM implementation by growers to high levels (Carriere et al., 2005, 2012; US Environmental Protection Agency, 2014; Tabashnik et al., 2013). Regulatory and government policies can also be adopted that encourage the development of insect protection products with favorable resistance risk profiles, such as those that have multiple modes of action and that incorporate refuge seed blended with GE insect-protected seed (Carroll et al., 2012; Head et al., 2014).

For regulatory and technology provider IRM programs to be fully effective, they must be embraced and promoted by all stakeholders that influence agricultural practices and growers' use of GE crops. Seed companies, retailers, and licensees are often the first source of information for growers on selection and management of their crop seeds, at both ordering time and delivery time. Public extension services and private crop consultants play an important advisory and management role for many growers and so need to promote consistent information for their clients. Grower groups and associations also play an important role in providing information and advice to their members. This is exemplified in the US by the National Corn Growers Association, which provides advice and educational tools for farmers growing GE corn (see http://www.ncga.com/for-farmers/best-practices/integrated-pest-management-practices). University and other public sector researchers have played, and continue to play, a pivotal role in developing data and other information that are the cornerstones of effective resistance management, and in promoting science-based resistance management programs with regulators, technology developers, and growers.

It is the mission of federal and state departments of agriculture to promote sustainable and efficient crop production; they play a key role in researching and advocating IRM for GE crops. For example, within the US Department of Agriculture (USDA), the Agricultural Research Service (ARS) conducts research into *Bt* resistance evolution; genetics and ecology of lepidopteran pests (at the Corn Insects and Crop Genetics Research Unit, Ames, IA); resistance evolution and characterization for corn rootworms (Plant Genetics Research Unit, Colombia, MO); and impacts of *Bt* resistance on cotton pest management (Southern Insect Management Research Unit, Stoneville, MS). USDA's National Institute for Food and Agriculture has supported research on resistance management for GM crops and works with ARS to fund biotechnology risk assessment grants. USDA's Economic Research Service studies adoption of GE crops and the economic impacts of resistant pests and resistance management programs. Such research programs provide valuable information that helps the design and implementation of effective, practical resistance management and mitigation programs for GE crops.

Conclusions: Resistance Management Supports the Sustainability of GE Crops

Genetically engineered crops have become important components of sustainable crop production systems. By reducing the need for soil tillage and insecticide applications while supporting high yields, they have boosted agricultural productivity and farm incomes while preserving ecosystem services and reducing the environmental footprint of agriculture (Brookes & Barfoot, 2012; Carpenter, 2011; Klumper & Qaim, 2014). These benefits have accrued in both developed and developing countries (James, 2010). Insect resistance management programs that are flexible, practical, and effective contribute to the ability of GE crops to help meet broader sustainability goals (National Research Council, 2010).

IRM programs for GE crops have been widely implemented for 20 years with a strong record of success (Tabashnik et al., 2014). The vast majority of insect pest populations remain susceptible to the insecticidal proteins that target them, and there is no documented field resistance in such economically impactful species as *Heliothis virescens, Ostrinia nubilalis*, and *Helicoverpa armigera* (Tabashnik et al., 2014). Resistance development tends to be associated with insufficient implementation of IRM programs, such as use of single-mode-of-action products without refuges. However, even where resistance has developed to one *Bt* protein, the resistant populations remain susceptible to one or more other *Bt* proteins. For example, *Spodoptera frugiperda* populations that are resistant to Cry1F are susceptible to Cry2Ab2 (Huang et al., 2014), and *Diabrotica virgifera virgifera* populations that are resistant to Cry3Bb1 remain susceptible to Cry34Ab1/Cry35Ab1 (Gassmann et al., 2014).

Continued innovation, enabled by past success and encouraged through appropriate regulations, will be needed to expand the benefits that have already been experienced. The first-generation single-mode-of-action insecticidal traits have now been largely replaced by crops with multiple proteins with differences in their modes of action. Along with technological innovations, the development and launch of new stewardship initiatives, such as the ETS IRM module, will continue to advance the role of GE crops in a sustainable agriculture that can provide food, fiber, and fuel for a growing global population.

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