Chapter 10
Sustainable Management of Insect-Resistant Crops

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Abstract Sustainability is a goal-oriented process that advances based on new knowledge. We discuss factors relevant to insect-resistant crops and sustainability: adoption patterns, insecticide use patterns and their influence on humans, biological control, areawide effects, and evolution of populations resistant to the transgenic crop. Genetically engineered insect-resistant crops were introduced at a time when insecticide options and use patterns were changing. Management of lepidopteran and coleopteran pests has been achieved through constitutive expression of proteins derived from the crystalline spore and the vegetative stage of various strains of *Bacillus thuringiensis*. Management to aphid-transmitted viruses has been achieved through expression of viral coat proteins. Adoption patterns have been rapid where use is allowed. Areawide reductions in pest populations have occurred in cotton and maize in multiple parts of the world, enabled eradication programs, and conferred significant economic benefits to crops that are not transgenic. Insecticide use has decreased dramatically in cotton, leading to improved biological control, reductions in pesticide poisonings, and changes in species composition that achieve pest status. Pro-active resistance management programs, the first to be deployed in all of agriculture, has slowed but not stopped the evolution of resistant populations. Five insect pest species have evolved resistance. Future constructs may provide induced or tissue-specific expression, or use RNAi to deliver protection from

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insect pests. Constructs that alter plant metabolism, to achieve drought tolerance, nitrogen-utilization, or biomass conversion efficiency, may also affect insect populations and communities. Sustainable management of insect-resistant transgenic crops requires consideration of regional effects of both densities and genetics of mobile target insect populations. The underlying assumption of IPM, that multiple and diverse management tactics are more sustainable, continues to be highly relevant, and necessary, to maintain the utility of transgenic crops, to manage the wider community of species relevant to agroecosystems, and to enable agriculture to adapt to change.

Keywords IPM • Areawide • *Bacillus thuringiensis* • Insecticide • Resistance

10.1 Introduction

Genetically engineered crops with resistance to insects or insect-vectored viruses have been used on over a billion acres worldwide since 1996. Commercial plantings include cotton, maize, potato, papaya and squash; potential commercial lines also exist for broccoli, eggplant, rice, and plum. Genes have targeted above- and below-ground herbivores from two taxonomic orders of insects, and successfully managed aphid-transmitted viruses. All of these examples—indeed, any change in plant phenotype—affect both the cropping system and the insect populations and communities that utilize those crops. The practice of Integrated Pest Management (IPM), rooted in the science of applied ecology and entomology, provides our context for describing effects on insect populations and communities. Here, we briefly summarize IPM and applied entomology concepts and existing transgenic crops, then discuss opportunities and challenges for their sustainable management at field, landscape, and regional scales.

10.1.1 Insect Resistance Traits

Insect resistance has been categorized as conferring antibiosis, antixenosis, or tolerance. Antibiosis traits directly reduce fitness of the insect, such as decreasing survivorship, prolonging development, or reducing fecundity. Plant expression may be continuous or induced (expressed in response to specific stimuli). Current commercially deployed transgenic crops that express proteins from *Bacillus thuringiensis* express constitutive antibiosis. The concentration of these proteins, however, varies within the plant, through time as the plant develops and senesces, and across the landscape depending on adoption patterns. The interaction of the protein concentration with the degree to which it affects insect fitness is critical to both effectiveness and sustainability of insect resistant crops. Engineering crops with induced antibiosis may be deployed in the future. Induced proteins would affect the spatio-temporal dynamics of insect exposure, and thus the selective pressure for resistance.

The additional categories—antixenosis and tolerance—also affect insect populations. Antixenosis refers to phenotypic traits that affect insect behavior, and tolerance refers to traits that affect the way in which the plant allocates resources to compensate for pest attack: for example, compared to older cultivars, modern cultivars of maize may produce higher grain yields in the presence of low to moderate amounts of stem-boring by lepidopterans (=caterpillars) due to a wide range of structural and biochemical traits that compensate for damage. Both the transgene that, for example, reduces survivorship of an herbivore, and other phenotypic traits that influence insect behavior and plant resource allocation, are integrated into elite hybrids during modern plant breeding. In addition, when considering insect-resistant crops in the future, it is important to realize that traits that may not be directly targeting insects, such as drought-tolerance or nutritional content, may also affect insect populations and communities through their affects on insect behavior and fitness.

10.1.2 Insecticides and Their Integration into IPM

Genetically engineered plants with insect resistant traits were commercialized while the types and availability of commercial insecticides were changing rapidly. Advances in insect physiology, toxicology, and formulation technology led to improved targeting and delivery of insecticidal molecules. Increased ecological and human safety is achieved, in part, through development of selective insecticides. Today's insecticides are classified into 26 chemical classes, and multiple subclasses, on the basis of their modes-of-action, defined globally.[1]

Insecticides made from the microbe *Bacillus thuringiensis* (*B.t.*) achieve high levels of selectivity. This microbe produces biodegradable protein crystals (termed Cry proteins), with typically three components (termed domains) during sporulation; some strains also produce additional insecticidal proteins during vegetative growth (termed vegetative insecticidal proteins, or VIPs). The Cry proteins separate into their domain subunits in the micro-environmental conditions of the insect gut, and subunits bind to protein receptors on the microvilli of the insect midgut lining. Effective binding results in pore formation and osmotic shock, which is followed by septicemia of the insect, probably involving microbes beyond the *B.t.* species. Selectivity is achieved through specificity of micro-environmental conditions, and binding properties of specific Cry proteins with specific receptor proteins, all associated with the insect gut. While the degree of selectivity varies, and thus some non-target species can be affected, high degrees of selectivity are common, often at the species level. Thus, a given Cry protein may be effective on one species of caterpillar but not a related species of caterpillar. Furthermore, effectiveness often

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[1] www.irac-online.org

varies with the life stage of an insect. Many *B.t.* materials need to be acquired by immature (larval) life stages, and are viewed as larvicides. Selectivity is further achieved through the requirements needed to deliver the protein to the target site: acquisition must be through ingestion, in contrast to modes-of-action that can be delivered through contact.

Over 250 insecticidal proteins have been recognized from *B.t.* The Cry proteins are classified by their amino acid sequence, with 67 major groups (Cry1 through Cry67), and additional subgroups defined by their evolutionary similarities.[2] For example, Cry1Ab, commonly used in agriculture, refers to category 1, subgroup A, and an additional subgroup b within A. Sprayable formulations of a few *B.t.* groups have been used for over 70 years in agricultural production, protection of stored grain, and mosquito control. Agriculturally relevant formulations have been derived from *B.t. kurstaki* (isolates produce CryIAb, Cry1Ac, or Cry2Aa,); *B.t. aizawai* (isolates produce Cry1Aa, Cry1B, Cry1Ca, or Cry1Da); *B.t. san diego* or *tenebrionis* (isolates produce Cry3Aa), and *B.t. kumamotoensis* (isolates produce Cry3Bb1). When *B.t.* is used as sprayable formulations, typically produced in fermentation culture, the *B.t.* insecticides require precise targeting because microbes can be sensitive to solar irradiation and they require ingestion by early insect life stages. By 1987 transgenic plants had been created that produced Cry proteins. This enabled efficient targeting of insects through ingestion by immature insect life stages. Commercial lines were first available in 1995.

The integration of insecticides with other tactics for insect management, notably biological control, driven by problems of resistance and additional species achieving pest status, was a primary basis for the emergence of Integrated Pest Management (IPM) programs during the last half of the twentieth century. An underlying assumption is that multiple and diverse management tactics are more sustainable when applied as a package than any one would be when relied on in isolation. A classic IPM pyramid (Fig. 10.1) shows a base, designed to minimize the effect of a pest upon the crop, built from knowledge of pest biology and ecology, biological control, host plant resistance, cultural control, and landscape factors. Monitoring, decision-making, and the use of insecticides in response to economically threatening population densities that have developed despite avoidance tactics are used in IPM. Insect resistance management (IRM) —efforts to delay the evolution of resistance— is also now formally integrated into IPM programs. Management may be at the field scale, or at larger geographic scales. Areawide management programs strive to remove, reduce, or slow the geographic expansion of pest populations at wide geographic scales. One way to focus the debate about the use of *B.t.*-transgenes is to ask if they represent host-plant resistance, or pro-active deployment of an insecticide. Both are true.

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[2] www.lifesci.sussex.ac.uk/home/Neil_Crickmore/B.t.

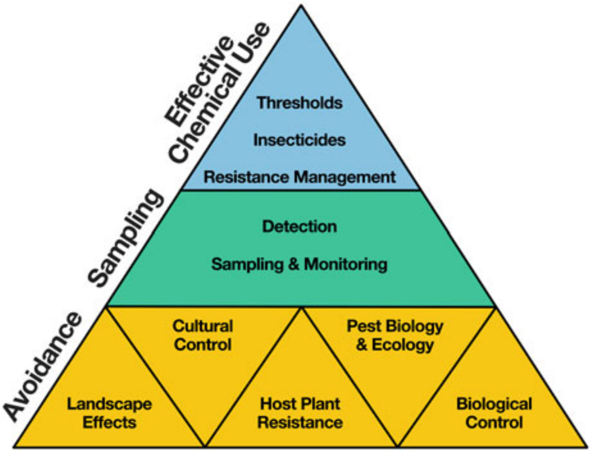

Fig. 10.1 Classic IPM pyramid (From Naranjo 2011, with permission)

10.2 The Emergence of Insect-Resistant Crops, Pyramids, Stacks, and Coupled Technologies

During the breeding process that leads to transgenic insecticidal plants, genes are isolated, connected to markers, and inserted into plants. The final construct after successful insertion is called an event, and government registrations are issued for specific events. Early constructs, and those still in use in some crops today, include a single event which codes for a single protein, such as Cry1Ab or Cry1Ac. Constructs can also be pyramided with multiple genes targeting the same pest (or a slightly overlapping group of related pest species), to broaden its activity and reduce the likelihood of resistance, or stacked with other traits such as herbicide tolerance. Pyramided constructs generally have different modes-of-action targeting the same species, and are replacing single gene plants because of their increased effectiveness. For example, the MON89034 event is a pyramided stack which codes for two Cry proteins, Cry1A.105 and Cry2Ab, targeting a group of lepidoterans. Increasingly, the insecticidal trait, conferred with either a single gene or through a pyramided event, is being stacked with events that confer herbicide tolerance.

Sweet corn provides a simple example. In the U.S., cultivars with the Bt11 event that codes for Cry1Ab have been in use since 1996. By 2012, cultivars became available with vector stacks that code for the Cry3Bb protein which confers resistance to rootworm larvae, plus CP4 which provides tolerance to glyphosate herbicide. Also, within the same cultivar, pyramided vector stacks became available in 2012 that produce Cry1A.105 and Cry2Ab, which provide resistance to several additional caterpillar species through different modes-of-action, and cultivars that include expression of VIPs are projected for commercial deployment soon.

Field maize presents a much wider array of transgenic cultivars. A summary in 2010 showed sources from 5 commercial enterprises provided 22 trait groups, some of which involve licensing agreements among several companies. All but one of these cultivars stacked insect resistance with herbicide tolerance. Insect resistance was conferred with nine different proteins, either singly, stacked, or pyramided in varying combinations, ranging up to five proteins aimed at insect pests from two different taxonomic orders. The range of Cry proteins expressed includes several from the Cry1A group, at least one Cry1F and one Cry2, several from the Cry3 group, and cultivars that express VIPs. Early cultivars provided resistance to moths in the family Crambidae. Newer stacks add resistance to several moth species in the family Noctuidae, and/or larval stages of beetles in the family Chrysomelidae with Cry3 proteins. Cry3 proteins had been introduced earlier, in potatoes in the mid-1990s, to control another Chrysomelidae species (Colorado potato beetle), and later potato cultivars included traits that conferred resistance to several aphid transmitted viruses, however these cultivars are not currently in use.

Simpler stacked and pyramided constructs are found in cotton, primarily because they target only lepidopteran pests. The initially introduced events were grown in a number of countries, and expressed a single Cry protein (Cry1Ac). Cry1Ac was then pyramided with either Cry1F or Cry2Ab2 to provide for better resistance management and to enhance the spectrum of efficacy within the lepidopteran group. China and India have cultivated a few unique events including a Cry1Ab + Cry1Ac pyramid and a pyramid involving a fusion protein (Cry1A) combined with a cowpea trypsin inhibitor. The addition of VIPs to several current constructs is underway by several companies.

Notable among insect-resistant crops beyond maize and cotton, China is developing insect-resistant rice with stacked and pyramided constructs, reviewed in Chen et al. (2011). As with maize and cotton, many of the insect-resistant events have been stacked with constructs conferring tolerance to several herbicides.

In addition to constructs modeled from proteins derived from *B.t.*, insect management is influenced by constructs derived from viral coat proteins (see Chap. 13). Expression of those coat proteins result in activation of a plant immune response, mediated by small RNA molecules, providing protection against infection by the virus of origin. This strategy has been used to achieve control of papaya ringspot virus in papaya since 1997, and one or more strains of four viruses in squash or zucchini since 1994. Aphids transmit these viruses by first acquiring them from an infected host. The virions adhere to receptor proteins in the needle-like mouthparts of the aphid. In subsequent feeding probes by the aphid, the virions are injected into a new plant. Where aphids pose a threat of pathogen transmission, tolerance of aphid populations by farmers is very low, resulting in a higher incidence of insecticide use. In contrast, when aphids do not pose a threat of pathogen transmission, tolerance of aphid feeding itself can be very high, and aphid management tends to rely primarily on biological control through natural enemies and entomopathogenic fungi. There are multiple other plants for which insect-transmitted plant-pathogenic viruses or bacteria can be controlled using transgenic methods, including apple, potato, and plum, but these have not moved into commercial production.

In addition to management of insect-transmitted pathogens, RNA-mediated processes are being developed to target insects that are direct pests of the plant, and mites that are parasites of honeybees. These involve a different mode-of-action than achieved with proteins. They can result in high degrees of specificity and can interfere with expression of specific genes in the insect (they are termed RNAi, for RNA-interference). Insect-resistant cultivars are also under development that stacks Cry or VIP proteins along with RNAi.

10.3 Sustainable Management of Insect-Resistant Crops

The agroecosystems in which transgenic crops are introduced are dynamic, and components do not operate independently. Transgenic crops often involve coupled technologies, including stacks or pyramids of insect-resistant genes and stacks of herbicide-tolerant genes. Transgenic as well as some non-transgenic cultivars are increasingly (currently almost always in the U.S.) being coupled with systemic insecticidal seed treatments, and may include seed coatings to help with mechanized planting, to protect against soil-borne pathogens, or as biostimulants that aim to induce up-regulation of resistance genes. Sustainability, which we recognize as a process with inherent goals and values, is affected by all of these technologies and their interactions with socioeconomic factors. Here, we illustrate factors particularly relevant to insect-resistant crops and the broad definition of sustainability: adoption patterns, insecticide use patterns and their influence on human welfare and biological control, areawide effects, and evolution of insect populations that are resistant to transgenic crops.

10.3.1 Adoption Patterns

Adoption patterns are defined overwhelmingly by social, political and economic factors. In maize and cotton, adoption rates are among the highest for any agricultural technology in countries where they are allowed. By 2011, adoption rates in five of the six largest cotton producing countries exceeded 70 % and *B.t.*-cotton comprised over 60 % of the world's production. *B.t.*-maize comprised 67 % of the U.S. crop in 2012.[3] Adoption of *B.t.*-sweet corn has been estimated at between 18 and 25 % among crops destined for fresh-market, but figures have not been available for the processing market. Adoption of transgenic papaya reached about 80 % in Hawaii, and 12 % of the squash in the U.S. utilized transgenes in 2005 (NRC 2010). In contrast, commercial sales of *B.t.*-potato in the U.S. were halted after about 6 years. These cultivars had resistance to Colorado potato beetle and several viruses, but processors declined to accept market risk, and growers tended to adopt systemic neonicotinoid insecticides that were introduced at the same time (NRC 2010). Neonicotinoid insecticides controlled a much broader array of insects and

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[3] www.ers.usda.gov/data/biotechcrops/

thus were easier to use with a much wider array of potato cultivars. *B.t.*-eggplant for use in India to control stem borers has been developed into commercially useful lines, completed regulatory reviews, and is projected to dramatically reduce insecticide use. Multiple *B.t.*-crucifer crops have advanced to commercially relevant lines, within the context of international public-private partnerships, although to date none are being produced commercially (see Shelton et al. 2008 for a good review of transgenic vegetables and fruit relevant to insect management). Market forces, political and business decisions, prohibitions, and labeling requirements, are among the primary factors slowing or stopping the commercialization of insect-resistant transgenes in vegetable and fruit crops. Insect-resistance achieved with genetic engineering techniques is totally prohibited in certified organic production for any crop, although the same *B.t.* proteins can be sprayed onto the plant. In cotton and maize, adoption rates are being influenced by the interest growers place on stacked traits such as herbicide-tolerance or traits aimed at multiple insect species. Adoption is also being influenced by the availability of seed: in some examples, seed without transgenic traits, or without stacked traits, may be hard to obtain. In the future, adoption rates may decline in response to decreasing pest populations resulting from areawide effects, discussed below.

10.3.2 Insecticide Use

Where insecticide inputs have been low on a per-acre basis prior to the adoption of transgenic cultivars, as in maize, changes in insecticide inputs are less clear, and may increase, in part due to the coupling of neonicotinoid seed treatments with transgenic crops. This coupling is a common, but not an inherent property of transgenic technology. Changes in use patterns are often driven by market factors interacting with factors driving the intensification of agriculture.

Insecticide use dramatically declined in cropping systems that were heavily dependent on insecticides prior to the introduction of transgenic crops, such as cotton. Reductions due to *B.t.*-cotton have been profound (Naranjo 2011). Debates that consider values inherent in sustainability are incomplete if they ignore these reductions and their implications. *B.t.*-cotton has reduced insecticide active ingredient use by 170.5 million kilograms between 1996 and 2010, with an associated 26 % reduction in the environmental impact quotient (a measure of the pesticide's impact on the environment and human health) (Brookes and Barfoot 2012). This has led to improved biological control of several pest species. Gains to human health can be dramatic when adoption of insect-resistant genotypes reduces insecticide use. Examples are well-documented in small-holder production systems. In India, where pesticide applications were reduced by 50 %, with larger reductions of the more toxic materials, *B.t.*-cotton is decreasing the incidence of pesticide poisonings by several million cases per year (Kouser and Qaim 2011). Studies also document fewer pesticide poisoning events in China and South Africa. Reductions of insecticide exposure to farm-workers and insecticide poisoning are consistent with values embedded in the process of sustainability. Socio-economic studies, controlled for other factors, have also documented improved dietary quality and caloric value, along with reduced food insecurity, among smallholder households that adopted *B.t.*-cotton (Qaim and Kouser 2013). The per-acre insecticide load is highest in vegetable and fruit crops, where manual labor is much more prevalent and insecticide problems related to human safety tend to be the most dramatic. Ironically, this is where market and regulatory forces are slowing development or adoption of insect-resistant transgenic cultivars. In a recent study in five US states across multiple years, *B.t.* sweet corn performed better and required fewer sprays than conventional sweet corn to meet market standards, thus reducing hazards to farm workers and the environment (Shelton et al. 2013). Unfortunately, debates about sustainability or desirability of transgenic crops rarely elaborate on effects on farm-workers.

10.3.3 Areawide Effects

If females deposit eggs equally among cultivars, and the transgenic cultivar reduces survivorship, then the transgenic cultivar acts as a population sink. The degree to which it drives down populations depends on rates of insect dispersal and adoption of the transgenic cultivar. For pink bollworm, a specialist herbivore, Carriere et al. (2003) showed adoption rates of about 65 % would drive down regional populations. Regional reductions have also occurred with polyphagous species, including *Heliothis virescens*, and to a lesser extent *Helicoverpa zea*, in cotton in the eastern U.S. In China, transgenic cotton dramatically reduced *Helicoverpa armigera* populations both in the cotton crop, and in the surrounding matrix of vegetable, corn, peanut, and soybean (Wu et al. 2008). Even in the presence of complex cyclic dynamics, Hutchison et al. (2010) documented how *B.t.*-maize reduced population growth rates of European corn borer, driving populations to historically low levels in large and multiple areas of the Midwestern U.S.

The areawide affects of *B.t.* plants are influencing IPM in ways relevant to values associated with sustainability. For pink bollworm, transgenic cultivars led to an organized eradication program that integrates transgenic cultivars with mating disruption via pheromone technologies, sterile insect release, cultural controls, and insecticides. Pink bollworm has been essentially eliminated from the U.S., and greatly reduced in bordering states of Mexico. While reductions in insecticides due to *B.t.*-cotton enabled other species (mirid bugs) to emerge into pest status, it also significantly increased populations of beneficial arthropod predators, which reduced herbivorous (aphid) prey populations, both in the cotton crop and surrounding maize, peanut and soybean crops in China (Lu et al. 2012). In combination with other IPM tactics, *B.t.* cotton in the western U.S. has dramatically enabled biological control of non-lepidopteran pests such as whiteflies and mirids and driven overall insecticide use down by nearly 90 %. In the Midwestern U.S., economic analyses considered effects to both land planted to *B.t.*-maize, and to the land planted to non-*B.t.* cultivars. Cumulative benefits were $3.2 billion in three states, with a surprisingly high percentage (75 %) accruing to non-*B.t.*-maize growers because the non-*B.t.* acreage did not carry the additional expense of the *B.t.*-seed. Similar high returns, and high fractions accruing to non-*B.t.* maize growers, occurred in an additional two states. Clearly, areawide effects—including eradication programs, reductions in insecticide use, increases in biocontrol, and economic savings—extend well beyond the boundaries of the planted crop.

Adoption patterns in the future could also be influenced by areawide effects. Theoretically, as populations decline, growers could shift to non-transgenic cultivars if they are available as elite hybrids, thus saving the appreciable cost of *B.t.*-seed, although some question if the non-*B.t.* hybrids will be available at a wide scale. Theoretically, both resistance management (discussed below) and maintenance of low populations could be achieved through spatio-temporal dynamics in adoption patterns at landscape and regional scales.

10.3.4 Evolution of Populations Resistant to the Transgenic Crop

Deployment of insecticides or insect-resistant germplasm has never been static. For example, to manage Hessian fly, over 60 wheat cultivars have been released with antibiosis resistance. The pest, in turn, has evolved over 16 biotypes that can overcome antibiosis, and management programs include variable spatial deployments of resistant germplasm. Insects are incredibly adaptable, and 550 species include populations with resistance to one or more insecticides. Sole reliance on antibiosis traits, regardless of the plant-breeding technology or insecticide mode-of-action, often creates a "treadmill": a race between evolution of resistance and new trait development and deployment. Models to help manage this evolutionary process were established prior to the deployment of transgenic crops. These models estimate time to acquire resistance, defined as an increase in the frequency of a resistant allele, as a function of life history, fitness, and population genetics. Simulations and experiments considered varying deployment options, and how they affected the time to acquire resistance.

Insect-resistant transgenic crops were deployed in the U.S. only after a resistance management plan was defined and accepted by the U.S. Environmental Protection Agency. Although heavily critiqued, and often lacking enforcement, to our knowledge this is the first, and only, regulatory-mandated use of resistance management plans prior to deployment of any technology in agriculture. These plans typically rely on refuges of non-*B.t.* hosts, and assume that alleles conferring resistance are rare, so that very few individuals survive on the *B.t.*-crop. The non-*B.t.* hosts provide a relatively large population of susceptible individuals, and the plans assume the rare survivor on the *B.t.*-crop will have a much higher probability of mating with a susceptible individual, resulting in individuals that are heterozygous for the resistant allele. Expression of *B.t.* is typically targeted sufficiently high to kill the heterozygote offspring. This is termed the “high-dose refuge” strategy. Additional assumptions inherent to the high-dose refuge strategy include random mating and single alleles conferring resistance. Additional factors that can contribute to delayed resistance include lower fitness or competitive abilities of individuals that manage to develop on the *B.t.*-crop. In the U.S. there have been many variations of refuge design, in terms of the percent of the crop (“structured refuge”), or non-crop alternative host (“unstructured refuge”), which serves as a source of susceptible individuals, and their spatial placement. The area required for planting to non-*B.t.* maize has varied from 5 to 50 %. For cotton, structured refuge has varied from 5 to 20 %. Spatial placements of structured refuges have varied from nearby blocks to seed mixes termed “refuge-in-a-bag”. Refuge requirements for pink bollworm were suspended as the eradication program was deployed, with the assumption that sterile male releases were providing susceptible phenotypes. In one case for *H. zea*, carbon-isotope studies documented that non-crop plants were providing susceptible individuals, leading to inclusion of “non-structured refuges” in resistant management plans under certain circumstances. Work with *B.t.*-crucifer crops as a model system demonstrated that deployment of pyramided constructs prior to the deployment of single constructs delays resistance, and pyramided deployments are becoming more common. For certain cotton cultivars planted east of west Texas, where unstructured refuges contributed susceptible phenotypes and the cultivars included pyramided resistant genes, the structured refuge requirement has dropped to 0 %. Stacked constructs aimed at multiple insect species require refuge designs appropriate to each of the targeted species, which can be difficult due to their differing behaviors (e.g., dispersal patterns and how that influences mating probabilities). Different life stages of the insect may have different susceptibilities to the resistant trait, which may also be expressed at variable levels within the plant or during the plant’s development, all of which affect the ability to consistently achieve a dose that kills heterozygous individuals. Thus, refuge designs change as new transgenic cultivars become commercialized, often with considerable debate among parties with conflicting interests.

Tabashnik et al. (2013) suggested that field-evolved resistance has been delayed when the allele conferring resistance has a low initial frequency, refuges are abundant, and pyramided toxins are used. They define resistance as the “ . . . genetically based decrease in susceptibility of a population . . . caused by exposure to the toxin in the field”, regardless of whether there are reductions in expected levels of control, or whether the insect was a pest that was expected to be controlled. By this definition, five insect species now include populations in specific locations that are resistant to *B.t.* crops. The degree to which this has affected pest control varies among populations and species. In maize, three species now exhibit sufficiently high resistance to a single protein in some populations to affect control. In the case of *B.t.* corn targeting corn rootworm larvae, the dose is not sufficiently high to meet criteria typically assumed to be necessary to achieve the “high-dose refuge” strategy, mating may not be random, resistance appears to be caused by more than a single allele and some of these may not be rare, and frequencies of fields with unexpected damage has recently been increasing. In cotton, two species have evolved a level of resistance to result in significant field damage in specific locations of the world and to specific events. In all five cases, plants with pyramided *B.t.* proteins are currently still effective, although the reduced selection process that should be conferred by separate modes-of-action may be compromised when the efficacy of one of the proteins is compromised There are additional cases where the frequency of resistant alleles has increased, but not at a level that has affected pest control as of 2013. Various tactics have been implemented to manage resistant populations when resistance resulted in significantly reduced field control. In the first clear case of resistance resulting in field failure, one case of resistance on a Caribbean island, the transgenic cultivar was removed from the market in Puerto Rico. In another, there has been increased emphasis on crop rotation, and rotation among cultivars that express different *cry* genes. There has also been increased emphasis on development and deployment of pyramided constructs and adherence to established refuge requirements.

10.4 Summary

Transgenic crops affect population densities of pest and beneficial insect species, biological control services, insecticide use patterns, pesticide poisoning of humans, and economics. Values relevant to discussions about sustainability exist for deployment of insect-resistant genetically engineered crops. Many examples document environmental and human health benefits in the first 17 years of adoption, which has been remarkably rapid where the technology has been allowed. The need for resistance management makes it clear that we are also dealing with effects on population genetics. The effects often occur at scales that transcend the land planted to the transgenic crop. Missing from many discussions, at least for vegetable and fruit crops, are effect on farm-workers. Sustainable management of insect-resistant transgenic crops requires consideration and management of regional effects of both densities and genetics of mobile insect populations.

The underlying assumption of IPM, that multiple and diverse management tactics are necessary to be more sustainable, continues to be highly relevant. Widescale adoption and over-reliance on only host plant resistance, especially when conferred via a single protein, creates exceptionally strong selection pressure, and insects have and will adapt with heritable changes in their genotypes and phenotypes. Insect resistance management (IRM), a component of IPM, is an integral part of deployment of transgenic cultivars. Sole reliance on a treadmill strategy with transgenic traits is not a sustainable strategy. Integration of insect-resistant traits with diverse pest management methods, through IPM, enables agriculture to also adapt and evolve, for management of the species targeted by the transgene(s), but also for the wider community of pest and beneficial species in the agroecosystems, and in the wider realm of changing markets, policies, and social and economic structures in which farmers operate.

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