Chapter 2
How Governmental Regulation Can Help or Hinder the Integration of *Bt* Crops within IPM Programs

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Abstract Regulatory risk assessments are an important part of the introduction of insect-resistant genetically modified (GM) crops (e.g., *Bacillus thuringiensis* [*Bt*] crops) into the environment to ensure the safe use of such products. In doing so, the regulatory assessment process can be clearly beneficial to integrated pest management (IPM) programs. In general, the regulatory framework for insect-resistant GM crops includes an assessment of the following: effects of the insecticidal trait on non-target organisms, other potential adverse environmental impacts, evolution of resistance to target pests, and environmental and agronomic benefits of the insecticidal trait. Each country's regulatory system is dependent on the overall environmental risk management goals, relevant and available risk information, scientific capacity, and the available financial resources. A number of regulatory activities can help to ensure that new products such as *Bt* crops fit well within IPM programs: (1) evaluation of the environmental safety of new products, and their ability to enhance IPM; (2) encouragement of the adoption of new technologies with improved environmental safety profiles; (3) adoption of an expedited regulatory review system; and (4) encouragement and appropriate oversight of sustainable use of such products. Governmental regulation of insect-resistant GM crops can also hinder IPM programs by creating significant barriers to the adoption of such technologies. Such barriers include: (1) absence of functioning regulatory systems in many developing countries; (2) meeting the obligations and understanding the various interpretations of international treaties, e.g., Cartagena Protocol on Biosafety; (3) lack of public sector research to generate data supporting the safety of these crops; and (4) regulatory costs involved in the development and commercialization of novel products for small market sectors. Ways in which regulatory data requirements can be globally harmonized need to be considered to decrease the regulatory

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J. Romeis, A.M. Shelton, G.G. Kennedy (eds.), *Integration of Insect-Resistant Genetically Modified Crops within IPM Programs.*

barriers for insect-resistant GM crops and comparable technologies. International organizations can play a key role in rationalizing regulatory systems; however, public sector research will also be needed to make sure that the risk assessment process is scientifically sound and transparent.

2.1 Regulatory Risk Assessment of *Bt* Crops

The regulatory framework for *Bt* crops in the United States of America and other countries has been developed and deployed within the broad context of risk assessment and integrated pest management (IPM). This framework typically includes consideration of environmental and agronomic benefits, such as reductions in applications of broad-spectrum insecticides, yield improvements and mycotoxin reduction in grain (USEPA, 2001a; Carpenter et al., 2002; Brookes and Barfoot, 2006; Cattaneo et al., 2006; Fernandez-Cornejo and Caswell, 2006; Fitt, chapter 11; Qaim et al., chapter 12). Furthermore, it includes assessments of the potential for the evolution of *Bt* resistance in target pests (Gould, 1998; USEPA, 2001a; Glaser and Matten, 2003; Tabashnik et al., 2003; Matten and Reynolds, 2003; Matten et al., 2004; Ferré et al., chapter 3), and effects on non-target organisms and other potential human and environmental impacts (USEPA, 2001a; Johnson et al., 2007). An assessment of environmental risk and management of insect resistance to *Bt* crops is critical to the sustainability of IPM programs.

2.1.1 The Nature of Regulatory Risk Assessment

An environmental risk assessment is conducted to facilitate regulatory decision-making with regard to identifying potential undesirable impacts and options for mitigating them. Assessing the potential for environmental risks of *Bt* crops, or any other insect-resistant crop, involves estimating the likelihood that the presence of the *Bt* gene(s) will have adverse effects on the environment. A risk exists if the exposure to the protein produced by the inserted gene has hazardous effects on non-target organisms. A risk assessment is a synthesis of sufficient information to determine whether the risks of a proposed course of action are acceptable. Estimates of potential hazard(s) and exposure allow regulatory decision-makers to determine the likelihood that a *Bt* protein, for example, may cause a problem and also to gauge the scale of that problem. There are several components of the environmental risk assessment that are particularly important: (1) Overall risk management goals and assessment endpoints; (2) Hazard identification; (3) Exposure identification; (4) Test endpoints; and (5) Iterative or tiered approach (Rose, 2007; Johnson et al., 2007; Raybould, 2007).

One of the more controversial areas of the regulation of *Bt* crops is post-market monitoring (PMM) after commercialization. In some parts of the world, for example Europe, it is required to monitor the environmental impacts of GM crops in commercial cultivation, as described in European Community Directive 2001/18/EC (EC,

2001). PMM includes both case-specific monitoring and general surveillance. Case-specific monitoring focuses on anticipated effects of a specific GM crop on the environment and aims to assess whether these effects do occur. A typical example for a case-specific monitoring area is insect resistance management of insect-resistant GM crops where major target pest populations are monitored to detect changes in the frequency of resistance alleles (USEPA, 2001a; Glaser and Matten, 2003; Tabashnik et al., 2003; Matten and Reynolds, 2003; Matten et al., 2004). General surveillance, in contrast, has the aim to detect adverse effects on the environment that were not anticipated during pre-market risk assessment. However, general surveillance lacks specific hypotheses concerning what one should monitor and why, as well as any baseline comparison to alternative practices such as the use of conventional pesticides. Therefore, the implications of finding an effect or change are unclear and causality to the cultivation of GM crops must be determined in separate risk assessment studies. Sanvido et al. (2005) describe a practical framework for the design of general surveillance of genetically-modified crops and propose to establish appropriate reporting systems to collect reports on adverse incidents that come from existing environmental monitoring programs. Ecological monitoring may also be conducted for a limited period of time to fill in data gaps (e.g., USA) or as a risk management option based on pre-market assessment of environmental risk.

2.1.2 Regulation and Insect Resistance Management

Insect resistance management (IRM) adds another dimension to IPM programs when *Bt* crops are deployed. IPM is one of the principal strategies for preventing resistance development because it uses diverse tactics to suppress pest populations and, conversely, IRM is a critical component of IPM programs because it ensures that important pest control tools remain viable for long-term use. In the USA, there has been substantial policy interest in maintaining the productivity of *Bt* as an important public resource to agricultural production systems, unlike any conventional pesticide (Berwald et al., 2006). One regulatory policy that attempts to maintain productivity of *Bt* is the institution of specific IRM requirements. Regulation of IRM for *Bt* crops is unprecedented in the pesticide world; there is no equivalent requirement for any conventional pesticide though the European Union (EU) recognizes the importance of pesticide resistance and requires registrants to address the risk of resistance development as part of dossiers submitted for EU registration (Anonymous, 2003; MacDonald et al., 2003). Voluntary IRM activities have been encouraged for conventional insecticides with some success. In the USA and Canada, for example, voluntary resistance management labeling guidelines for all agricultural pesticides based on the rotation of mode of action were developed as a joint activity under the auspices of the North American Free Trade Agreement (NAFTA). These guidelines were published as EPA Pesticide Registration Notice 2001–2005 (USEPA, 2001b) and Canada Pesticide Regulatory Directive DIR 99–06 (Health Canada, 1999). While the EU, USA, and Canada have adopted a

combination of mandatory and voluntary approaches to regulating insect resistance to chemical insecticides, the role of mandatory approaches is one of great debate amongst the various stakeholders from industry, grower organizations, academia, and government (Thompson and Head, 2001).

IRM strategies for *Bt* crops differ among countries based primarily on the target pests, agricultural practices, cropping patterns, adoption of the technology, and cost. Both mandatory and voluntary regulatory systems are in place in countries where *Bt* crops are grown. Mandatory IRM programs are required in the USA, Canada, and Australia, for example. In contrast, voluntary IRM programs exist in China, for example. At a global level, some form of baseline susceptibility/monitoring studies are conducted in all countries prior to commercialization. Regardless of the country, the basic elements needed to develop and implement an IRM plan remain the same: (1) knowledge of pest biology and ecology; (2) toxin dose; (3) the genetics of potential resistance; (4) cropping patterns and potential use of the *Bt* crop; (5) baseline susceptibility; (6) a resistance monitoring plan; (7) grower education; and (8) remedial action plan should resistance develop. Simple field studies, work on model systems, and simulation models can allow for a qualitative comparison of possible IRM strategies. The area of IRM requirements for *Bt* crops has not been without controversy and has stimulated much interest among academic researchers, government, industry, and growers. IRM programs for *Bt* crops are discussed in several other chapters in this book in general (Ferré et al., chapter 3), for maize (Hellmich et al., chapter 5), for cotton (Naranjo et al., chapter 6), for potato (Grafius and Douches, chapter 7), and for rice (Cohen et al., chapter 8).

The overall environmental risk management goals, relevant and available risk information, and the technical tools available influence the way *Bt* crops are regulated in each country. This chapter focuses on how regulatory systems can either enhance or hinder the use of *Bt* crops within an IPM program, and provides insights into regulatory issues that will arise from non-*Bt* insect-resistant crops developed in the future (Malone et al., chapter 13).

2.2 Regulation as an Enhancement to IPM Programs

Government regulation helps to ensure that new agricultural pest-control products will fit well into IPM programs in a number of ways, either through explicit consideration of IPM needs or because of common objectives between environmental regulations and IPM. We discuss some of these direct and indirect positive impacts of regulation on IPM programs in the sections below. These impacts are not specific to *Bt* crops, or other products of biotechnology, but rather will apply to any technology being considered for commercial use in agriculture. Due to the rapid and widespread adoption of *Bt* crops on a global level, *Bt* crops represent the most important set of novel insect control technologies to be approved by regulatory agencies in the last two decades.

2.2.1 Regulatory Assessments Focus on the Environmental Safety of New Products

In assessing the environmental safety of any *Bt* crop, governmental regulatory agencies explicitly consider the potential risk posed to various groups of non-target organisms. For example, before allowing a *Bt* crop to be grown commercially, data on the risk posed to representatives of economically and ecologically important guilds such as organisms important for biological control (predators and parasitoids such as ladybird beetles, lacewings, and parasitic wasps), pollinators (such as honeybees), and organisms involved in soil processes (such as springtails and earthworms) are reviewed by agencies such as the United States Environmental Protection Agency (USEPA) and the United States Department of Agriculture (USDA) in the United States, and the European Food Safety Authority (EFSA) in the European Union, and comparable agencies in other countries (Rose, 2007). These risk assessments focus on non-target organisms that are locally important and require data generated in the relevant crop and country. By ensuring that new technologies will not have significant adverse impacts on these non-target groups, regulatory agencies indirectly ensure that these technologies also will fit well into IPM programs, complementing biological control functions and minimizing non-target pest flare-ups. By applying such standards, regulatory agencies also encourage the development of future pest control technologies with these characteristics.

2.2.2 Regulatory Assessments Encourage the Advancement of Technologies with Improved Environmental Profiles

In the environmental risk assessment process carried out by regulatory agencies, the potential risks associated with these new agricultural pest control technologies generally are compared with the observed impacts of alternative pest control technologies that farmers may currently use. For *Bt* crops, these alternative technologies usually will be conventional insecticides. These assessments of relative risk help to ensure that *Bt* crops and other new pest control technologies being introduced are superior, or at least equivalent, to existing technologies in their environmental profiles. In doing these assessments, the components of agro-ecosystems that are examined and the criteria that are applied are largely coincident with the needs of IPM programs, and thereby ensure that new technologies, such as *Bt* crops, will be useful additions to existing IPM programs. For instance, environmental impact quotients (EIQ) for *Bt* crop systems typically have been found to be significantly lower than the EIQs for alternative technologies such as conventional insecticides (Kleter et al., 2007). EIQ is a measure designed to summarize the impacts of a pesticide on various ecosystems components, as well as effects on human health. As a consequence, no significant adverse environmental effects have been associated with the global adoption of *Bt* crops (Sanvido et al., 2007), while the technologies

that they have replaced (i.e., insecticides) often had adverse impacts on the environment and human health (for example, Naranjo et al., 2005; Wu and Guo, 2005; Cattaneo et al., 2006; Qaim et al., chapter 12).

2.2.3 New Technologies with Superior Environmental Profiles Can Be Fast-Tracked

Because environmental agencies are focused on the impact of pest control technologies on the environment, they often have developed specific mechanisms to expedite the approval of environmentally safer pest control alternatives to conventional chemical pesticides, such as *Bt* crops. For example, in the USA, the Pesticide Registration Improvement Act of 2003 promotes shorter decision review periods for applications for reduced-risk. At the same time, approvals for the use of products with unfavorable environmental profiles may be withdrawn. For example in the USA, the Federal Food, Drug, and Cosmetic Act was amended in 1996 to include the Food Quality Protection Act or FQPA. This Act required EPA to reassess by August 2006 all of the pesticide tolerances that were in place in early August 1996 to ensure that they met current safety standards and were supported by up-to-date scientific data. FQPA also mandated a registration review process. Every 15 years, EPA will reassess each pesticide to see whether it still meets the registration standards required under the Federal Insecticide, and Rodenticide Act (FIFRA). The net effect of these initiatives will be to provide safer tools for IPM programs.

2.2.4 Sustainable Product Use Can Be Encouraged

As regulatory agencies identify and approve the use of new environmentally friendly technologies, they also look for ways to ensure that these products are used in a sustainable way so that their continued availability is assured. In the case of *Bt* crops, regulatory agencies such as the US EPA have worked with the product developers to construct and implement IRM programs for each product that will serve to delay the evolution of target pest resistance and thereby protect the durability of these products (Gould, 1998; Glaser and Matten, 2003). These IRM programs have included the implementation of structured non-*Bt* refuges and resistance monitoring programs and, in the case of the United States, Australia and India, the replacement of single *Bt* gene cotton (Bollgard I®) with the more durable dual *Bt* cotton (Bollgard II®) when it became available. IRM programs have now been implemented for *Bt* crops on a world-wide basis in both developed (for example, USA, Canada and Australia) and developing countries (such as India and the Philippines). Many of these programs were initially implemented voluntarily by the product developers in these countries; however, they now are typically required by regulators as part of regulatory packages for *Bt* crops in most countries. IRM activities have aided IPM programs by ensuring

that effective and reliable tools are available for sustainable control of certain key lepidopteran and coleopteran pests. IRM programs for *Bt* crops have contributed to mitigating field resistance to *Bt* crops in the world during the past decade (Tabashnik et al., 2003; Ferré et al., chapter 3). While IRM programs have been invaluable, programs that are effective for one or more target pests in one geographical region may not be as effective against other economically-important pests in other geographical regions. A case in point is the recent report of fall armyworm (*Spodoptera frugiperda*, J.E. Smith) resistance to the Cry1F protein expressed in TC1507 maize fields in 2006 in Puerto Rico. Fall armyworm is the most important pest of maize in Puerto Rico where the tropical climate allows year-round production of maize and multiple pest generations each year. The mountainous island also creates a more closed pest population than is the case for other pests and other geographies. In 2007, USEPA reviewed unpublished data submitted by Dow AgroSciences and Pioneer Hi-Bred International that detailed their investigation of unexpected fall armyworm damage found in TC1507 maize fields in 2006 in Puerto Rico and whether such damage was caused by resistant insects (Matten, 2007). Based on review of the screening level and concentration-dependent bioassays, the conclusions was that the unexpected performance failures of TC1507 maize observed in 2006 in Puerto Rico were due to Cry1F-resistant fall armyworm. Because of this finding, sales of this product have been suspended in Puerto Rico, consistent with the IRM program. Fall armyworm resistance to TC1507 maize is much less likely to occur in the continental USA because it can only overwinter in the extreme south of Texas and Florida, and therefore, selection in maize-growing regions exerts no long term selection pressure.

2.3 Regulation as a Hindrance to IPM Programs

While the goals of environmental regulation often have much in common with IPM goals, regulation can hinder IPM programs by creating significant barriers to the introduction of important new technologies under certain conditions. This is particularly true of products of agricultural biotechnology such as *Bt* crops because of the specific and complex regulatory systems that have been created to deal with these products. Unfortunately, the barriers created often are greatest where the technologies are potentially most needed, for example in developing countries in Africa and Asia (Gressel et al., 2004; Thomson, 2008). The circumstances under which regulation can adversely affects IPM programs are discussed below.

2.3.1 The Absence of Functioning Regulatory Systems in Many Developing Countries

Experience to date with *Bt* crops has shown that they can play a role in the implementation of IPM practices in developed and developing countries (Obando-Rodriguez et al., 1999; Bambawale et al., 2004; Sanvido et al., 2007; Kennedy,

chapter 1). However, a critical step in the application of these crops is the regulatory approvals that must be obtained before they can be used, based on appropriate risk assessments by regulatory authorities. Therefore, a sound and functional regulatory system must be established before the full potential of these crops can be realized. This system must be capable of making the necessary scientific evaluations in order to arrive at a reasoned and scientifically supportable decision. However, a regulatory decision also ultimately involves non-scientific issues to a greater or lesser extent. Regulatory systems should be able to manage non-science issues, such as labor (Shelton, 2007), in such a way that appropriate and beneficial technologies are not prevented from reaching the market.

Functional biotechnology regulatory systems are largely absent in most developing countries. In Africa, for example, relatively few have established biosafety frameworks. According to the Biosafety Clearinghouse mechanism of the Cartagena Protocol on Biosafety, only 14 countries on the African continent have written laws, regulations, guidelines, or policies concerning genetically engineered crops (http://bch.cbd.int). With the exception of South Africa, which has approved *Bt* maize and *Bt* cotton for commercial release (http://www.agbios.com/dbase.php), none of those countries have had experience in the assessment of applications for commercialization of any genetically engineered plant variety. Consequently, their ability to conduct a risk assessment connected with an application for commercial release of a *Bt* crop has yet to be tested. By contrast, more developing countries in Asia have established functioning regulatory systems. China and India have commercialized *Bt* cotton, while the Philippines has commercialized *Bt* maize (James, 2007). The absence of a regulatory system, or even one that has demonstrated functionality, has prevented many developing countries from experiencing the benefits that have been experienced by those countries where *Bt* crops have been approved. Most of these countries have not even been able to conduct confined field trials to determine efficacy or conduct studies that are prerequisites for any regulatory decision concerning these crops.

There are many reasons for the absence of functional regulatory systems in developing countries, but a primary factor is the lack of scientific capacity in many regulatory agencies. Risk assessment to support regulatory decisions requires a multi-disciplinary approach, encompassing such fields as toxicology, eco-toxicology, genetics, molecular biology, chemistry, taxonomy and ecology. While most developing countries possess expertise in many of these fields, few of them have expertise in the complete range of scientific disciplines that may be required, particularly within the regulatory agencies themselves. Furthermore, many developing country regulatory systems are composed of part-time members rather than full-time professional staff, a situation made necessary by the lack of government resources to support such a staff, and because of the involvement of a broad range of government ministries. Broad representation requires capacity building in ministries staffed by decision makers, many of whom do not possess the basic understanding of the biological disciplines underlying the development of *Bt* crops. Even in those ministries and scientific bodies involved in the process that may have the necessary expertise, the focusing of this expertise into the discipline of risk assessment requires capacity building as well.

2.3.2 Meeting the Obligations of International Treaties

At the international level, the Cartagena Protocol on Biosafety (CPB) has the potential to further hinder the introduction of *Bt* crops. While the original intent of this international agreement was to facilitate the safe trans-boundary movement of genetically engineered crops and other commodities, in order to assure fair and equitable access to the benefits of biotechnology (Cartagena Protocol on Biosafety to the Convention on Biological Diversity, 2000), elements of the implementation of this protocol could, in some countries, severely affect the transfer of this technology. Primary among these elements is the implementation of Article 27 of the CPB, regarding the establishment of rules and procedures concerning liability and redress. The negotiations surrounding this provision of the CPB are at a critical stage, and fundamental questions regarding such issues as the scope of this provision (whether limited to damage to biodiversity or more broadly to traditional and socioeconomic damage), the definition of who is liable, the limits of liability, and the requirements for insurance, have implications for the introduction of genetically engineered crops. For example, if liability were to be extended to developers of genetically engineered crops for an indefinite period of time, and for an indefinite amount (a possible scenario under the current negotiations), the sharing of *Bt* crops developed in countries that are party to the CPB with other party countries could be severely restricted. Similar effects would be seen on crops developed in non-party countries as well. This is particularly problematic because most countries that are parties to the CPB are developing countries that have invested heavily in public sector research to develop genetically engineered local crops to address local needs. The sharing of the benefits of this research between developing countries would be severely affected by overly restrictive liability regimes.

2.3.3 Special Barriers to Products Coming from the Public Sector

For the private sector, significant experience has been gained over the years in the procedures to generate data supporting the safety of these crops. On the other hand, the public sector has had very little experience in the commercialization of transgenic crops. There are only two examples of transgenic crops developed by the public sector – papaya and plums – and these examples do not provide good guidance for the regulatory requirements governing *Bt* crops. Unlike *Bt* proteins, the viral coat protein expressed by the transgenic papaya have no known toxicity (Gonsalves et al., 1996), and therefore do not raise questions of hazard to non-target organisms. The plum transgenic lines do not produce detectable levels of protein (Scorza, 2004). Therefore, questions about the impact of a novel protein on the environment – a major consideration with *Bt* crops – were not even considered in these cases.

Public sector initiatives face additional hurdles in trying to introduce new technologies with IPM applications. These hurdles are exacerbated by the cost of the regulatory approval process. The regulatory requirements for *Bt* crops, because they have been based to a large degree on the requirements covering conventional pesticides, have imposed significant costs on the approval process, estimated to be between $7 million and $15 million for *Bt* maize for approval in ten major market countries (Kalaitzandonakes et al., 2006, 2007). Thus, approval in even one country could cost between $700,000 and $1.5 million. This cost is well beyond the reach of public sector projects, even in the developed world. Therefore, if current regulatory models continue to be applied to *Bt* crops, the ability to develop these crops on a worldwide basis, particularly those that address developing country needs, will be hindered. Developing country public research is focused on crops for the poor, and therefore is a government investment, with returns coming back to the public in less definable ways – food security, better health, greater subsistence farmer income – than for a product developed by the private sector. The challenge, therefore, especially for developing country regulatory agencies, is to examine where data requirements can be reduced or streamlined without compromising the level of safety achieved by current developed-world regulatory requirements, in order that the investments made by governments are fully realized.

2.3.4 Barriers to Developing Products for Small Markets

Because of the regulatory costs currently involved with *Bt* crops, it is difficult for either the public or private sector to develop novel products specifically for small markets, including specialty crops in the developed and developing world and almost any crop in countries with relatively small agricultural sectors. However, efforts involving private-public partnerships may prove fruitful in bringing some *Bt* crops like eggplant and vegetable crucifers to market in India and other developing countries (Shelton et al., chapter 9). Technologies developed primarily for use in other systems or countries may still make it into these smaller markets, but this will dramatically limit the problems that can be addressed through biotechnology in the short term. Many developing countries urgently need safe and reliable pest control alternatives, and *Bt* crops provide a good solution to these needs. Here, too, adaptations to existing regulatory systems and standards will need to be considered if the benefits of *Bt* crops and comparable technologies are to be more broadly realized.

2.4 Future Considerations

Regulatory risk assessments are an important part of the introduction of any new agricultural technology, and can help to ensure that new technologies meet certain standards with respect to environmental safety. In doing so, the regulatory assessment

process can be clearly beneficial to IPM programs, but a balance between regulatory rigor and efficiency must be achieved. Functioning regulatory systems need to adequately assess the potential risks associated with new technologies but should not be so burdensome as to be a barrier to the introduction of valuable technologies. This balance is more difficult to reach when resources and scientific capacity are more limited, as is the case in many developing countries.

Ways to harmonize regulatory requirements across regions and to allow data generated in one country to be recognized in other countries will need to be investigated if pest management programs in developing countries are to fully realize the benefits of *Bt* crops (Romeis et al., 2008). For example, laboratory data showing that there is an absence of a toxic effect of a particular Cry protein on a certain non-target specific is generally valid and could be used for risk assessments in any country. International organizations like the Organization for Economic Cooperation and Development (OECD) can play an important role in rationalizing regulatory systems. Public sector scientists will also need to make sure that their voices are heard as part of this process.

Disclaimer

The views expressed in this article are those of the individual authors and do not necessarily reflect the views and policies of the US Environmental Protection Agency, Monsanto Company, or Crop Technology Consulting, Inc. The use of trade names does not imply endorsement by the US Government.

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