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REVIEW

Bt crops and food security in developing countries: realised benefits, sustainable use and lowering barriers to adoption

Alan Raybould · Hector Quemada

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Abstract Transgenic crops producing insecticidal proteins from the bacterium *Bacillus thuringiensis* (*Bt* crops) have been cultivated commercially for over 15 years. Worldwide, *Bt* crops have provided effective control of target pests with fewer applications of insecticide, have increased yield and profitability for farmers, and have reduced risk to the environment and human health compared with non-*Bt* crops. Sustainable use of *Bt* crops requires risk management to limit the evolution of pest resistance and adverse effects of the *Bt* proteins to non-target organisms. Risks are managed by national regulatory authorities; however, the establishment of functional regulatory systems with the necessary scientific capacity is problematic in many developing countries, which hinders the wider deployment of *Bt* and other transgenic insect-resistant crops. Timely introduction of these crops may also be obstructed by inefficient implementation of international regulatory regimes, such as the Cartagena Protocol on Biosafety (CPB). Regulatory costs limit the number of insect-resistant crops that may be developed, and delay in the introduction of such crops may result in large opportunity costs. Implementing effective risk management while limiting these costs requires clear policy that defines the benefits and harms of cultivating transgenic crops and how those benefits and harms should be weighed in decision-making. Policy should lead to the development of regulatory frameworks that minimise the number of new data requirements and maximise the value of existing studies for risk assessment; costs will thereby be reduced, increasing the prospects for *Bt* crops, and transgenic insect-resistant crops generally, to improve food security in developing countries.

Keywords *Bacillus thuringiensis* · Insect control · Transgenic crops · Regulation · Risk assessment

A. Raybould (✉)
Syngenta, Jealott's Hill International Research Centre,
Bracknell, Berkshire RG42 6EY, UK
e-mail: alan.raybould@syngenta.com

H. Quemada
Donald Danforth Plant Science Center,
975 North Warson Road,
St. Louis, MO 63132, USA
e-mail: hquemada@danforthcenter.org

Introduction

The global demand for food is likely to increase for at least the next 40 years (Godfray et al. 2010). Part of this increased demand could be met by reducing the "yield gap" — the difference between yields achieved using the best seeds and agronomic management and those actually achieved on the farm (Huang et al. 2002). A significant proportion of the yield gap results from damage to crops by animal pests, such as insects, mites, nematodes, gastropods, birds, rodents and other mammals. Oerke (2006) estimated that on average, between 15 and 20% of crop yield could be lost to animal pests worldwide, but that actual losses to these pests were reduced to about 10% because of pest control measures.

Following their introduction immediately after the Second World War, synthetic insecticides have played an important part in increasing crop yields by reducing losses to pests (Thacker 2002). Their use does present problems, however, and the early indiscriminate use of insecticides caused adverse effects on non-target organisms, outbreaks of secondary pests (Newsom 1967; Metcalf 1980) and quickly led to evolved resistance in the target pests (Roush and McKenzie 1987). In developed countries, modern chemicals with narrower spectra of activity, along with lower application rates, have greatly reduced adverse environmental effects of insecticides (Nauen and Bretschneider 2002; Thacker 2002); however, in developing countries, adverse effects, particularly to human health, are still common owing to the use of older chemistries, and laxity in the preparation, application, storage and disposal of chemicals, which may result from poor training and weak occupational health regulations (Ecobichon 2001). High rates applied as a response to widespread resistance to many insecticides in serious pests such as *Helicoverpa armigera* (cotton bollworm) (Martin et al. 2002) may also contribute to adverse effects of insecticides in developing countries.

Transgenic crops producing insecticidal proteins offer a means to control insects without the potential harmful effects from the misuse of synthetic insecticides; in particular, because incorrect preparation and application of insecticides are avoided as they are already within the crop. Some of the first transgenic crops intended for commercial use were genetically engineered to contain genes from the soil bacterium *Bacillus thuringiensis* (*Bt*) (Demont and Tollens 1998; Perlak et al. 2001), and currently all commercialised transgenic insect-resistant crops contain active ingredients derived from *Bt*. *Bt* has been used as a biopesticide since the 1930s, mainly to control lepidopterous pests of forestry and agriculture, and the larvae of mosquitoes and fly species that are vectors of serious diseases of humans and livestock (Beegle and Yamamoto 1992).

The principal active ingredients of the microbial *Bt* pesticide formulations are crystal (Cry) proteins produced in large amounts in the spores of the bacterium (Agaisse and Lereclus 1995). Cry proteins were of particular interest to the developers of the first transgenic crops because they are highly potent and have relatively narrow spectra of activity, and therefore offered the potential for efficacious insect control with few non-target effects and low environmental residues (Betz et al. 2000). Cry proteins are produced as protoxins that are activated by proteases in the insect gut. The activated toxins bind to receptors in the insect gut, which leads to the formation of pores in cells of the gut lining. Subsequently, the cells undergo lysis, leading to death of the insect by septicaemia (Bravo et al. 2007). The narrow spectrum of activity of individual Cry proteins results from variation among insects in gut pH, protease activity and receptor structure (De Maagd et al. 2001). Other insecticidal proteins from *Bt*, such as vegetative insecticidal proteins (Vips), have similarly attractive properties for developers of insect-resistant transgenic crops (Estruch et al. 1996; Lee et al. 2006).

Worldwide, the cultivation of transgenic crops is strictly regulated under laws that already existed to control the use of pesticides and plant pests or that were created specifically to control the use of transgenic plants (Jaffe 2004). Potatoes producing Cry3A to control Colorado potato beetle gained regulatory approvals and were first cultivated commercially in the United States in 1995; maize and cotton producing Cry1A proteins to control various lepidopterous pests were also granted regulatory approvals in 1995 in the United States, and were first cultivated there the following year (De Maagd and Bosch Stiekema 1999; Mendelsohn et al. 2003) (Table 1). Subsequent approvals include Cry1F and Vip3A for control of Lepidoptera in maize and cotton, Cry2Ab for control of Lepidoptera in cotton, and Cry3Bb, Cry34/35 and mCry3A in maize to control corn rootworm (Gatehouse 2008). There are many other *Bt* proteins that have potential commercial use, including native Cry proteins such as Cry1C (Avisar et al. 2009) and engineered chimeric Cry proteins such as eCry3.1Ab (Walters et al. 2010).

Crops producing Cry proteins (*Bt* crops) have provided effective control of target pests with fewer applications of insecticide, which has contributed to increased profitability for farmers (Naranjo 2009). This article reviews the extent to which the benefits of *Bt* crops have been realised in developing countries, how those benefits may be sustained, and how barriers to further beneficial use of *Bt* crops in developing countries may be lowered. Application of these ideas more generally may help to maximise the benefits from other transgenic insect-resistant crops that are in development, but have not been commercialised. A variety of non-*Bt* insect-control genes has been genetically engineered into crops (Malone et al. 2008), but none has been commercialised, and the lessons learned from *Bt* crops may help to realise the potential benefits from other types of transgenic insect resistance.

Benefits of *Bt* crops in developing countries

In 2009, *Bt* crops were grown commercially in 23 countries, of which 16 are developing countries (Table 1). The primary benefit of planting *Bt* crops has been the improvement of yield and farm profitability, particularly in comparison with corresponding non-*Bt* varieties in comparable circumstances. This benefit has been obtained by farmers in developing and developed countries (Qaim and Zilberman 2003; Huesing and English 2004; Raney 2006; Yorobe and Quicoy 2006; Qaim 2009); however, because of local conditions and variability of pest pressure and other environmental factors from year to year, decreased performance relative to non-*Bt* varieties has been reported in some cases, with consequent impacts on profits (Bennett et al. 2006; Raney 2006; Qaim et al. 2006). The increase in yield appears to result from protection against insect damage because the same yields can be obtained from non-*Bt* varieties if pesticides are applied (Cattaneo et al. 2006).

Table 1 The use of *Bt* crops in developed and developing countries. Developing countries are those on the World Bank's 2009 list

Developed countries	Crop	Main target pests	Environmental approval or first cultivation
United States	Potato	Colorado potato beetle	1995
	Cotton	Cotton[†] and pink bollworms, tobacco budworm	1996
	Maize	European corn borer, western corn rootworm	1996
Canada	Potato	Colorado potato beetle	1995
	Maize	European corn borer, corn rootworm	1997
Australia	Cotton	Cotton bollworm[‡]	1996
Spain	Maize	European corn borer, Mediterranean corn borer	1998
Czech Republic	Maize	European corn borer	2005
Portugal	Maize	European corn borer, Mediterranean corn borer	2005
Slovakia	Maize	European corn borer	2006
Developing countries			
China	Cotton	Cotton bollworm[‡]	1997
	Rice	Asiatic rice borer	2009
Mexico	Cotton	Cotton[†] and pink bollworms, tobacco budworm	1997
South Africa	Maize	African stem borer, pink stalk borer	1997
	Cotton	Cotton [‡], red and spiny[*+] bollworms	1998
Argentina	Cotton	Cotton[†#] and pink bollworms, tobacco budworm, cotton leafworm	1998
	Maize	Fall armyworm, sugarcane borer	1998
Honduras	Maize	Fall armyworm	2001
India	Cotton	Cotton[‡], pink, spiny[+] and spotted bollworms,	2002
Chile	Maize	Fall armyworm	2002
Philippines	Maize	Asian corn borer	2002
Colombia	Cotton	Cotton[†#] and pink bollworms, tobacco budworm, cotton leafworm	2003
Uruguay	Maize	Fall armyworm	2003
Brazil	Cotton	Tobacco budworm, pink bollworm	2005
	Maize	Fall armyworm	2007
Poland	Maize	European corn borer	2006
Romania	Maize	European corn borer	2007
Burkina Faso	Cotton	Cotton bollworm[‡]	2008
Egypt	Maize	Durra stem borer, European corn borer, purple-lined stem borer	2008
Costa Rica	Cotton	Cotton[†#] and pink bollworms, tobacco budworm	2009

African stem borer = *Busseola fusca*

Asian corn borer = *Ostrinia furnacalis*

Asiatic rice borer = *Chilo suppressalis*

Colorado potato beetle = *Leptinotarsa decemlineata*

Cotton bollworm = *Helicoverpa armigera*[‡], *H. gelotopoeon*[#] and *H. zea*[†]

Cotton leafworm = *Alabama argillacea*

Durra stem borer = *Sesamia cretica*

European corn borer = *Ostrinia nubilalis*

Fall armyworm = *Spodoptera frigiperda*

Mediterranean corn borer = *Sesamia nonagrioides*

Pink bollworm = *Pectinophora gossypiella*

Pink stalk borer = *Sesamia calamistis*

Purple-lined stem borer = *Chilo agamemnon*

Red bollworm = *Diparopsis castenea*

Spiny bollworm = *Earias biplaga*[*], *E. insulana*[+]

Spotted bollworm = *Earias vittella*
Spotted stalk borer = *Chilo partellus*
Sugarcane borer = *Diatraea saccharalis*
Tobacco budworm = *Heliothis virescens*
Western corn rootworm = *Diabrotica virgifera*

Carpenter (2010) analysed peer-reviewed studies of *Bt* crop yields. In developed countries, the average increase in yield from *Bt* maize compared with conventional maize was 4%, with a range between -3% and 13%; in *Bt* cotton, the average yield increase was 7%, with a range between −8% and 26%; and in *Bt* cotton with transgenic herbicide tolerance, the average yield increase was 3%, with a range between −3% and 9%. In developing countries, the yield increase for *Bt* over conventional crops was higher: the average increase in yield for *Bt* yellow maize was 16%, with a range between 0% and 38%; for *Bt* white maize, the average yield increase was 22%, with a range between 0 and 62%; and for *Bt* cotton, the average yield increase was 30%, with a range between −25% and 150%.

Qaim (2009) and Carpenter (2010) also analysed profitability of *Bt* crops; increased yield may not necessarily be associated with increased profitability because higher yields may have been achieved with higher costs, or lower yields with lower costs. In the 80 examples of the profitability of *Bt* crops analysed by Carpenter, 59 showed an increase with *Bt* crops, 14 a decrease and 7 showed no difference. As with yield, increases in profitability have been larger in developing countries, particularly in *Bt* cotton: the average increase in gross margin in Australia and the United States was US$66/ha in Australia and US $58 in the United States, whereas in Argentina, China, India, Mexico and South Africa, the average increases in gross margin were 23, 470, 135, 295 and 91 US$/ha, respectively. The difference between developed and developing countries for increases in profitability provided by *Bt* maize is less clear: maize farmers in Spain increased their gross margin by 70 US$/ha and those in the United States increased theirs by 12 US$/ha, whereas gross margin increased by 20, 53 and 42 US$/ha for *Bt* maize farmers in Argentina, the Philippines and South Africa, respectively (Qaim 2009). Although Carpenter's and Qaim's analyses do not present the statistical significance of the average increases in yield and profitability for *Bt* crops, both authors conclude that trends in the data indicate benefits for farmers from the technology, and that the benefits are greater in developing countries.

While increases in yield and gross margin are important, food security will be improved most effectively by reducing poverty, for example by increasing employment and household incomes. There are few studies of such wider socio-economic impacts of cultivating *Bt* crops (Qaim 2009), but initial indications are that the impacts are beneficial. Subramanian and Qaim (2009, 2010) analysed the socio-economic impact of *Bt* cotton cultivation on a single Indian village using data on the direct effects of *Bt* cotton and a social accounting matrix to simulate indirect effects. The simulations indicated that cultivation of *Bt* cotton was associated with increased employment: while there was less requirement for labour to control pests, this was more than offset by increased labour required for harvesting increased yields of cotton. An interesting effect of the switch from pest control, which is largely carried out by men in the family of the farmer, to harvesting, which tends to be done by hired female workers, is that women earned more than men from *Bt* cotton. Nevertheless, men were able to use the time saved from controlling pests to carry out other agricultural and non-agricultural work, and so they also benefited from *Bt* cotton. Overall, agricultural and non-agricultural workers benefited in terms of increased employment and income, with greater benefits to those employed in agriculture, and larger farms benefiting more than smaller farms. Subramanian and Qaim (2009) postulate that the effect of farm size results from farmers on larger farms being better educated and having more resources to exploit savings in time spent managing the cotton, and they suggest that improved access to education and finance would increase the benefits of *Bt* cotton to farmers on smaller farms.

In contrast, a study of smallholder farmers in South Africa (Shankar and Thirtle 2005) concluded that the adoption of *Bt* cotton did not result in a change in the labour required to grow that crop. The same offsetting effects on labour requirements observed in India were also identified in the South African case; however, because the South African farmers used relatively little pesticide, the reduction in labour for pest control was consequently less, and was balanced by the increased labour to harvest the increased yields. Only modest gains in labour savings for South African smallholders were also reported in a subsequent study (Hofs et al. 2006). These examples illustrate the importance of local farming practices and other agricultural constraints on the magnitude of socio-economic benefit realised from the adoption of *Bt* crops.

In addition to beneficial effects on yield and profitability, *Bt* crops have had positive impacts on the environment and on human health. *Bt* crops have allowed farmers to reduce the amount of insecticide applied (Brookes and Barfoot 2005, 2007, 2008, 2010). Worldwide, the greatest savings in absolute terms are associated with *Bt* cotton, because it was the crop on which the highest amount of synthetic insecticide was applied (Sanvido et al. 2007). Brookes and Barfoot (2010) estimate that between 1996 and 2008, the use of *Bt* cotton was associated with a reduction in insecticide use of just over 140 million kg of active ingredient, a decrease of 21.9%. *Bt* maize was associated with a reduction of nearly 30 million kg of insecticidal active ingredient, a decrease of 35.3%.

Studies of individual countries have shown similar results. In the United States, the country with the highest level of adoption, insecticide application on cotton was reduced by 28–53% in Arizona in 2002 and 2003 (Cattaneo et al. 2006). More recent data on *Bt* maize and cotton throughout the US show comparable trends (Johnson et al. 2007b; National Research Council 2010). Large reductions in insecticide use have also been experienced in developing countries: China and Mexico realized 60%–70% and 80% reductions, respectively (Huesing and English 2004). These data are similar to figures on reduction of pesticide costs — between 41% and 77% — reported for Argentina, China, India, Mexico and South Africa (Raney 2006). Qaim (2009) reported reductions in pesticide use of between 33% and 77% in surveys of *Bt* cotton in Argentina, Australia, China, India, Mexico and the United States; and between 0% and 63% for *Bt* maize grown in Argentina, the Philippines, South Africa, Spain and the United States.

Brookes and Barfoot (2010) converted the change in insecticide use into a change in the environmental impact quotient (EIQ). The EIQ is an index for comparing the impact of pesticide applications on people applying the pesticide, consumers who may ingest pesticide residues, and on the environment. Variables used to calculate an EIQ include the persistence, toxicity and application rate of the pesticide, which are combined to give an EIQ per hectare for a pattern of use of the pesticide (van der Werf 1996). Worldwide, between 1996 and 2008 the EIQ associated with *Bt* cotton was 24.8% less than that for conventional cotton, and the EIQ for *Bt* maize was 29.4% less than that for conventional maize. Overall, 93% of the reduction in EIQ for *Bt* cotton and 2% of the reduction in EIQ for *Bt* maize were contributed by developing countries (Brookes and Barfoot 2010).

The reduction in pesticide use has resulted in increased biodiversity within *Bt* fields compared with non-*Bt* fields treated with conventional insecticides (Marvier et al. 2007; Duan et al. 2008; Wolfenbarger et al. 2008; National Research Council 2010). One benefit of higher biodiversity may be the improved natural control of other pests, which has been reported in the case of aphids in cotton in China. The use of insecticides in non-*Bt* cotton fields reduces the populations of aphid predators, while allowing those predators to survive in *Bt* fields; therefore, improved control of aphids by natural predators is seen in *Bt* fields (Wu and Guo 2003). Higher biodiversity in *Bt* fields is not always beneficial, however, because pests other than the target pest may increase in abundance as insecticide use is reduced (see below).

Another benefit of the deployment of *Bt* crops has been the reduction of pest insect populations on a regional scale. This phenomenon has been observed in the US, for example with pink bollworm and *Bt* cotton in Arizona (Carrière et al. 2003), with consequent benefits for non-*Bt* crops that may also be susceptible to the pests targeted by the *Bt* crops (National Research Council 2010). Studies in China found similar area-wide suppression of cotton bollworm associated with *Bt* cotton, also with benefits to non-*Bt* crops (Wu et al. 2008).

Human health benefits have also been documented for *Bt* crops. Reduced synthetic insecticide use in cotton in China has resulted in reduced pesticide exposure, which in turn has reduced cases of pesticide toxicity (Huang et al. 2002; Pray et al. 2002; Hossain et al. 2004; Huang et al. 2005). Reduction in physical injury to stems and kernels of *Bt* maize by lepidopterous pests has reduced the level of secondary fungal infections, thus reducing the accumulation of mycotoxins produced by those fungi. This reduction has been observed in studies from the US and other countries (Munkvold et al. 1999; Williams et al 2002; Hammond et al. 2004; de la Campa et al. 2005; Brookes 2008; Folcher et al. 2010; Ostry et al. 2010). The clearest evidence for reduction is in the fumonisin mycotoxins; however, *Bt* maize also appears to have the potential to reduce aflatoxin, deoxynivalenol and zearalenone (Wu 2007). While developed countries place strict controls on mycotoxin levels in grain, developing countries have fewer resources to control such toxins and therefore should benefit more significantly from this effect of *Bt* maize.

Sustaining the benefits of *Bt* crops

There are two important problems that may limit the durability or extent of the benefits of *Bt* crops. First, previously susceptible insects have become resistant to microbial *Bt* formulations (Tabashnik et al. 1990; Janmaat and Myers 2003), which raises the possibility of resistance evolving to the proteins produced by *Bt* crops (Bates et al. 2005). Secondly, the control of primary pests by the *Bt* crop may lead to outbreaks of secondary pests that that are no longer controlled by the many insecticide applications previously used to control the primary pests; for example, in some parts of China, the abundance of mirid bugs is higher in *Bt* cotton than in non-*Bt* cotton because they are often not effectively controlled by the fewer insecticide applications used to control cotton bollworm in *Bt* cotton (Wu et al. 2002; Lu et al. 2008; Lu et al. 2010). Secondary pests are often particularly problematic when insecticide applications remove biological control organisms that are predators or parasitoids of the secondary pests (Newsom 1967; Metcalf 1980). Biological control organisms are also a useful additional source of control of the primary pests and may reduce the probability of resistance evolving (McGaughey and Whalon 1992); therefore, possible adverse effects of *Bt* proteins in transgenic crops on biological control organisms have also been an area of interest for ecological risk assessment of *Bt* crops (Dale et al. 2002; Romeis et al. 2006).

Insect resistance management

Insects are notorious for quickly evolving resistance to insecticides (Roush and McKenzie 1987). During regulatory review of *Bt* crops in the United States, there was much discussion about preserving the effectiveness of *Bt* proteins in transgenic crops, particularly because farmers using conventional or organic methods often rely on *Bt* microbial formulations for insect control. It was decided, therefore, that use of *Bt* proteins in transgenic crops should be managed to reduce the risk of insect resistance evolving and thereby prolong the effectiveness of *Bt* insecticides as a public good that might be irreplaceable (McGaughey et al. 1998).

Insect resistant management (IRM) plans for *Bt* cotton and maize used the so-called high-dose — refuge strategy. This strategy assumes, among other things, that resistance to the *Bt* protein is controlled by a single gene, and that alleles conferring resistance are recessive and rare, and therefore almost all resistance alleles are present in heterozygotes. The *Bt* crop delivers a high dose of *Bt* protein that is many times greater than the concentration required to kill heterozygotes carrying resistance alleles. The refuge part of the strategy requires farmers growing *Bt* crops to plant a certain amount of non-*Bt* crop to act as a refuge for susceptible insects, so that any resistant homozygotes emerging from the *Bt* crop will mate with a susceptible homozygote (Mendelsohn et al. 2003). The progeny of the resistant individuals will, therefore, be heterozygotes and highly susceptible to the high dose of *Bt* protein in the crop, preventing the increase in the resistant allele frequency and outbreaks of resistant genotypes that could cause the *Bt* crop to fail (Bates et al. 2005).

Other countries that have approved the cultivation of *Bt* crops have adopted high-dose — refuge strategies similar to those introduced in the United States, sometimes with additional elements such as restricting planting times of *Bt* crops, limiting insecticide use in the refuge, and cultivating immediately after harvest (MacIntosh 2010). Where there are many alternative host plants of the pests targeted by the *Bt* crop, such as for *H. armigera* in *Bt* cotton in China, there may be no requirement for a structured refuge because sufficient susceptible insects are produced in the “natural refuge” of alternative hosts (Liu et al. 2008).

IRM plans for *Bt* maize and cotton targeting lepidopterous pests appear to have worked well in the continental United States; although there are reports of increases in resistance allele frequencies in *Helicoverpa zea* in *Bt* cotton producing Cry1Ac (Tabashnik et al. 2008); the significance of these results is disputed and, furthermore, there are no reports of widespread failures of *Bt* crops (Moar et al. 2008). Nevertheless, there are cases of *Bt* crop damage that are reportedly the result of field resistance of pests: *Busseola fusca* (African stem borer) in Cry1Ab maize in South Africa (Van Rensburg 2007); *Spodoptera frugiperda* (fall armyworm) in Cry1F maize in Puerto Rico (Moar et al. 2008); and *Pectinophora gossypiella* (pink bollworm) in Cry1Ac cotton in India (Haq 2010), although this last case is not yet reported in the peer-reviewed literature.

Analysis of the development of *S. frugiperda* resistance to Cry1F maize suggests that the crop may not have delivered a high dose allowing resistance to evolve rapidly through a non-recessive mechanism; multiple yearly generations of *S. frugiperda* may also have hastened resistance (Matten et al. 2008; Tabashnik et al. 2009). Resistance of *B. fusca* to Cry1Ab maize in South Africa appears at some sites to have resulted from poor-quality refuges producing insufficient susceptible insects and from non-compliance with refuge requirements at other sites (Van Rensburg 2007; Kruger et al. 2009). An alternative explanation is that some populations of *B. fusca* in South Africa were relatively insensitive to Cry1Ab before the introduction of *Bt* maize; this possibility is suggested by work showing that populations of *B. fusca* in Kenya are only partially controlled by experimental *Bt* maize lines producing Cry1Ab and Cry1Ba (Tende et al. 2010).

Whether evolution of resistance is more likely in developing than developed countries depends upon the influence of opposing factors. It is possible that different crop and pest biology and non-compliance with refuge requirements make the evolution of resistance to *Bt* crops more likely in developing than developed countries; however, smaller plot sizes as well as the increased possibility of alternate hosts in the form of other crops or non-cultivated species, may make the evolution of resistance less likely. Whatever is the case, first-generation *Bt* crops are considered vulnerable by regulators in developing countries, even those with the best-run IRM programmes, because the crops rely on a single active ingredient to control target pests. Combining in a single plant two or more proteins with activity against the same target pests, a procedure called “pyramiding”, is recognised as an effective method to increase the durability of efficacy of *Bt* crops. It is important, however, that the proteins target different receptors in the insect gut so that the possibility of cross-resistance is minimised (Roush 1997).

Several types of *Bt* cotton are available with pyramided proteins that have different receptor sites of action: Bollgard® II from Monsanto, which produces Cry1Ac and Cry2Ab (Perlak et al. 2001); Widestrike™ from Dow, which produces Cry1Ac and Cry1F (Blanco et al. 2008); and VipCot™ from Syngenta, which produces Cry1Ab and Vip3Aa19 (Kurtz et al. 2007). Cross-licensing of insect control traits among companies allows the possibility of cotton and maize containing proteins with 3 sites of action against some lepidopterous pests to be commercialised soon (Gatehouse 2008).

Owing to the lower probability of resistance evolving simultaneously to two or more proteins with different sites of action, the US EPA and authorities in Australia have reduced refuge requirements for cotton with pyramided insect-resistance genes compared with cotton with single-gene resistance; for example, in some parts of the United States no structured refuge is required (MacIntosh 2010). The development of *Bt* crops with pyramided insect-control proteins offers developing countries the possibility of more durable efficacy against insect pests than might otherwise have been achieved with *Bt* crops with single proteins targeting certain pests. These crops may help to mitigate problems of pest biology, farmer education and refuge compliance that could undermine IRM efforts in developing countries; however, deployment of pyramided *Bt* crops should not mean that farmer education and compliance are redundant in developing countries, simply that IRM should be more resilient to any weaknesses in these activities.

As with any risk management strategy, the costs of the management, including opportunity costs, must be balanced against the benefits of reducing risk. The mathematical models on which the high-dose refuge strategy was based were conservative because they assumed 100% adoption of a *Bt* crop with only one type of *Bt* protein. Most *Bt* crops will be grown in spatially complex landscapes, including *Bt* crops with different *Bt* proteins, that are likely to reduce greatly the probability of resistance evolving compared with monocultures of a single crop with a single protein. Over-reliance on conservative models, which for example may suggest that pyramids are always to be preferred to crops with one protein, may hinder the development of crops with new modes of action that reduce the likelihood of resistance evolving (Storer et al. 2008). Furthermore, long-term protection of a technology by restricting its use does not necessarily outweigh short-term benefits of widespread use, particularly if the development of new products is encouraged by such a policy.

Biological control

Microbial *Bt* has a reputation as an effective insecticide for quite specific applications, but its general use is restricted because, among other things, it has a narrow spectrum of activity and requires an oral route of exposure (Navon 2000), which limits its cost-effectiveness (Wainhouse 2005). *Bt* formulations can have adverse effects on biological control organisms in laboratory studies (Flexner et al. 1986), but in the field any adverse effects can be minimised by careful timing of application (Navon 2000). From the point of view of assessing the risks of *Bt* crops to biological control, studies that found adverse effects of *Bt* formulations on biological control organisms are difficult to interpret: the microbial formulations contain mixtures of many toxins and inert ingredients, whereas *Bt* crops produce one or a few pure toxins. In general, purified Cry proteins have few adverse effects on insects outside the order of the target pest (Van Frankenhuyzen 2009) and therefore *Bt* crops were expected to pose minimal risk to biological control functions, especially when compared with applications of synthetic insecticides.

Risks to biological control from deployment of *Bt* crops are tested using a framework similar that for synthetic pesticides (Romeis et al. 2008). First, the *Bt* crop is assessed for unintended changes in composition that may harm non-target organisms; the compounds analysed may be nutrients, anti-nutrients or toxins depending on the crop. Despite the scientific and technical problems associated with animal feeding studies, they have been used in the past to support the evidence from compositional analysis that harmful changes in composition have not occurred (Kuiper et al. 2001). If no potentially harmful changes are detected, the risk assessment can concentrate on the likelihood that the intended production of the *Bt* protein(s) will harm biological control. If potentially harmful unintended changes are detected, such as an amount of an endogenous toxin that is outside the normal range of the crop, that change can be assessed in further studies.

The likelihood that a *Bt* protein in a transgenic crop will cause environmental harm is evaluated in a series of laboratory effects tests that expose various species to the protein. The species tested are representative surrogates for species likely to be exposed to the *Bt* protein in the field *via* cultivation of the *Bt* crop. Concentrations of the *Bt* protein in the laboratory tests are set to be higher than the worst-case exposures that will result from cultivation of the crop. If no adverse effects on the surrogate species are observed under these conditions, one may be confident that there will be no adverse effects on any species exposed to the *Bt* protein in the field[1]. Although field trials are more realistic than laboratory studies, they are less rigorous tests of the hypothesis of no adverse effects of the *Bt* protein because organisms are exposed to lower concentrations of *Bt* protein

[1] A similar rationale is used for assessing the risks to human and animal health from consumption of products derived from *Bt* crops. A full description is outside the scope of the paper and readers are referred to Kuiper et al. (2001) for a review of this subject

than in the laboratory; therefore, if no adverse effects are observed in the laboratory, field studies should not be required to assess the risks to biological control organisms from cultivation of the *Bt* crop.

Few, if any, laboratory studies done under international guidelines for regulatory submissions have detected adverse effects of Cry proteins on biological control organisms (Mendelsohn et al. 2003; Raybould et al. 2007). Despite the lack of adverse effects in the laboratory, many field studies to assess the effects of *Bt* crops on biological control organisms have been undertaken to confirm that predictions from laboratory studies are reliable. All indications are that laboratory studies accurately predict field-scale effects of *Bt* crops on biological control organisms (Romeis et al. 2006; Marvier et al. 2007; Duan et al. 2010), and that therefore currently available *Bt* crops pose negligible risk to biological control.

Laboratory studies of the effects of *Bt* proteins on non-target organisms have been done largely in American and European laboratories on American and European species; nevertheless, these data are often applicable to risk assessments for *Bt* crops in developing countries. Although non-target organism faunae in developing countries may contain different species from those in developed countries, provided that the taxonomic and functional groups likely to be exposed to a particular *Bt* protein are adequately represented by the existing effects studies, it should not be necessary to perform additional laboratory studies on that protein with non-target species from developing countries; nor should it be necessary to carry out field studies specifically to measure effects on non-target organisms in developing countries. Field studies to measure agronomic performance and insecticidal protein concentration should be sufficient to complete an effective environmental risk assessment (Romeis et al. 2009).

Lowering barriers to increased uptake of *Bt* crops

Regulatory and scientific capacity

To achieve the benefits of *Bt* crops, approvals for commercial cultivation must be obtained, based on suitable risk assessments by regulatory authorities. A sound and functional regulatory system must therefore be established before the full potential of these crops can be realised.

Regulatory systems that can approve commercial deployment of *Bt* crops — or indeed any transgenic crop — are lacking in most developing countries. In Africa, for example, only 10 countries have “functional” biosafety frameworks (Karembu et al. 2009). Of these, only three — South Africa, Burkina Faso and Egypt — have approved transgenic crops for commercial cultivation; therefore, most African countries that apparently have a framework to handle an application for commercial release of a *Bt* crop have not yet applied that system. Similarly in Asia, only China, India and the Philippines are currently growing *Bt* crops (James 2009). Most developing countries have not even progressed to the stage of conducting confined field trials, which are prerequisites for determining local efficacy and for generating any other local information that may be required for commercial approvals.

One important reason for the absence of fully capable regulatory systems is lack of scientific capacity in many developing country regulatory agencies. Risk assessment requires a multi-disciplinary approach, involving expertise in such fields as toxicology, ecotoxicology, genetics, molecular biology, chemistry, taxonomy and ecology. Many developing countries do not possess expertise in all of these disciplines, especially within the regulatory agencies themselves. Furthermore, many developing country regulatory systems are staffed by part-time members, and many decision-makers lack a basic understanding of the biological disciplines underlying the development of *Bt* crops. For those regulators and decision-makers who possess the necessary expertise, training in focusing this expertise for the purpose of risk assessment is required; external expertise is available to assist them build capacity in risk assessment through resources provided by groups such as the Program for Biosafety Systems (PBS), and the African Biosafety Network of Expertise (ABNE).

Another potential barrier to the successful deployment of *Bt* crops is the effect of certain provisions of the CPB. The manner in which countries interpret and implement Article 27 of the CPB, regarding the establishment of rules and procedures concerning liability and redress, is of particular concern. Extreme liability provisions implemented by countries that are parties to the protocol may appear to them to be prudent, but would instead prevent their own researchers from developing transgenic crops, including *Bt* crops, because those researchers would be unable to bear the burden of liability. This problem is especially severe in developing countries, because they are the most reliant on meagrely funded public research programs to produce the transgenic crops that are needed locally. Extreme liability regimes could also affect the ability of charitable donors to fund *Bt* crop development. It is unlikely that donors will be able or willing to risk a high exposure to a strict liability regime, which would significantly increase the cost of operations, and limit or eliminate the availability of funding to achieve useful impact.

Public sector developers of transgenic crops lack the experience in product development and regulatory affairs that is needed for successful commercialisation. Because the public research sector is the primary avenue for the development of these crops, including *Bt* crops, there is a significant gap in expertise that must be filled in order to enable their adoption. Furthermore, the cost of regulatory approvals may pose an additional significant barrier. One study estimated the cost of regulatory approval to be between US$7 million and US$15 million for Bt maize for approval in ten major market countries (Kalaitzandonakes et al. 2006; 2007). The cost for even one country (US$700,000 to US $1.5 million) would be beyond the reach of many public sector projects, especially in the developing world. A separate study has arrived at a similar estimate (US$1.4 million) for regulatory compliance and meeting government regulatory compliance in the Philippines for the *Bt* maize event MON 810 (Manalo and Ramon 2007). Interestingly, pre-approval compliance costs have been estimated at US $1.8 million for the first *Bt* cotton event approved in India, while in China, regulatory costs were calculated to be significantly less, at US$53,000 to US$61,000 each for *Bt* cotton varieties, to US$89,500 each for *Bt* maize varieties (Pray et al 2005, 2006).

The cost of regulatory compliance poses a policy challenge for developing country regulatory agencies. Not only are there costs associated with meeting regulatory requirements, but the lost opportunity costs should be considered as well. For example, a 2-year acceleration in the regulatory process for *Bt* cotton in India would have increased farmer revenue by US$300 million (Pray et al 2005). For the Philippines, regulatory delays in the deployment of *Bt* rice could theoretically cost US$26 million in benefits for a 1-year delay, up to US$76 million for a 3-year delay (Bayer et al. 2010).

As the reported costs for China show, the cost of gaining regulatory approvals for transgenic crops can be significantly reduced below amounts required for regulatory approvals elsewhere. It is therefore possible for regulatory agencies to carefully assess the regulatory data requirements necessary to assure a proper safety evaluation, and avoid those that do not help decision-making. In particular, developing countries should fully exploit data produced for regulatory approvals of transgenic crops in developed countries while avoiding flaws in the regulatory frameworks in some of those countries.

The relationship between science and policy in risk assessment

In some developed countries, notably those in the European Union, concerns about possible adverse impacts of cultivating transgenic crops have delayed their introduction and limited their use. Often in these countries, extensive data are requested in addition to those supplied to regulatory authorities in the countries where the crop was first commercialised; however, additional studies appear not to help decision-making, but to increase confusion and concern about transgenic crops (Johnson et al. 2007a). There are several possible reasons for this, but misunderstanding the purpose and role of science in risk assessment seems to play a large part.

A common mistake is to view risk assessment as an activity that should describe completely the possible results of cultivating and processing transgenic crops; thus, much effort may be spent searching for and characterising slight differences between the phenotype and management of the transgenic crop and non-transgenic comparators without a clear idea of how such information will help decision-making. A more fruitful approach is to regard risk assessment as a prediction of the likelihood that something harmful will result from cultivation or use of the transgenic crop. In effect, a risk assessment is a test of a hypothesis that there is an acceptable probability that certain harmful effects will not occur; and if existing data have corroborated that hypothesis sufficiently, there is no need to collect additional data to characterise more precisely all possible effects of cultivating the crop (Raybould 2007). Estimates of the probability and seriousness of harmful effects are far more useful to decision-makers than a catalogue of possible effects.

A likely reason for the misunderstanding of the purpose of risk assessment is repeated emphasis that it is an objective scientific activity and should eliminate non-scientific considerations (e.g., McHughen 2007). The problem with this approach is that what is regarded as harmful must be defined subjectively by policy (Sagoff 2005); we cannot discover what to regard as harmful scientifically. Once harm has been defined, science can analyse the probability that an activity will result in that harm; however, if harm is undefined, we cannot discover what to regard as harmful by scientific research into the likely effects of the activity. By eliminating non-scientific considerations, harm is not defined at the beginning of the risk assessment, and instead, the risk assessment seeks to discover what to regard as harmful by exhaustive characterisation of the crop and its associated management. The farm-scale evaluations in the United Kingdom (Firbank et al. 1999) were a clear example of this approach. If the only purpose of a study is for risk assessment to help decision-making, it is crucial that the study tests for effects that predict harm, otherwise resources are wasted studying phenomena of no relevance to estimating risk. In addition, opportunities to rigorously test for effects that indicate harm may be missed because the experiments are not designed for that purpose. It is essential, therefore, that risk assessment studies follow from definitions of harm set out in policy and do not attempt to discover harm by simply measuring anything and everything about the transgenic crop; that only leads to wasted resources and ineffective risk assessment (Raybould 2007).

As countries develop definitions of harm, it is important to recognize that the potential for harm from agriculture is not unique to transgenic crops (National Research Council 2002). The fact that even conventionally bred crops and current agricultural practices cannot meet the standard of absolute safety is embodied in the CPB itself, which explicitly makes consideration of the risks posed by non-transgenic organisms one of the general principles of risk assessment. Consideration of current agricultural practice is a useful device for risk assessment: if current practice is considered to pose acceptable risk, risk assessments for transgenic crops can be formulated to test hypotheses that their cultivation and use pose no greater risk than current practice; however, if this approach is adopted, it is essential that the potential harmful effects of current practice are made explicit, otherwise the risk assessment will default to a comparison of effects, not a characterisation of whether the likelihood and seriousness of harm are greater than posed currently.

Recognising that risk assessment is not a purely scientific activity may help to reduce barriers to the introduction of *Bt* crops in developing countries. It is essential that risk assessors and regulators in developing countries make maximum use of existing data before requesting new data from crop developers. Existing data are likely to be most effective when decision-makers have clearly set out what would be regarded as harmful effects of cultivating the crop in their country. Risk assessors can then use existing data to test hypotheses that cultivation and use of the transgenic crop are unlikely to lead to those effects. Only if risk assessors decide that existing data do not test those hypotheses sufficiently rigorously, should they request additional data. Consequently, the lowering of barriers to the introduction of *Bt* crops will depend on science being led by clear policy; in the absence of policy, scientific studies may give the impression of worthwhile activity to assess risk, but in fact they will raise barriers because they will increase costs with no beneficial effect on decision-making.

Conclusion

Bt crops help to achieve food security in developing countries by providing higher yields of food crops and by increasing the profitability of farmers growing food and non-food crops. Alongside the higher yields and profitability, *Bt* crops are associated with improvements in the environment and in human health resulting from reduced use of synthetic insecticides. Maintaining and widening the benefits of *Bt* crops in developing countries will depend on the effective assessment of risk to the environment and human health from the cultivation and use of *Bt* crops, and on the implementation of adequate IRM plans, but without unnecessarily high regulatory barriers that may stifle the development of *Bt* crops suitable for local needs. It will also be important to strengthen the ability of developing country regulatory systems to access the appropriate scientific expertise and to use that expertise in a disciplined application of risk assessment principles.

Achieving the best combination of risk management, product stewardship and encouragement of the development of new *Bt* crops for developing countries may be difficult and controversial; however, it is clear that the search for the right combination of these factors requires the development of policy, and cannot be just a matter of scientific or technical analysis. Policy should clearly describe the benefits sought by the use of *Bt* and other transgenic crops, what would be regarded as harmful effects of growing the crops, and how regulatory decisions will be made in the light of assessments of the probability that specific benefits and harms will arise should a particular crop be cultivated. Clear judgements about the benefits and harms of transgenic crops should also avoid over-zealous interpretations of international agreements, such as the CPB, that may place insurmountable obstacles in the way of the development of these crops, particularly by harming the ability of local researchers to develop transgenic crops for local needs.

While science can assess the probability of certain results of growing transgenic crops, it cannot tell us whether to regard those results as beneficial or harmful; therefore, it is important that science is not used as a displacement activity for making regulatory policy. Effective deployment of *Bt* and other transgenic crops in developing countries will be achieved by the creation of regulatory frameworks that deliver policy objectives, and which guide the collection of scientific data that are needed for decision-making. It is likely that effort spent defining benefits and harms, and how they should be set against each other when making decisions, will be more than repaid by the avoidance of scientific studies that duplicate those done elsewhere, that are done because of extremely conservative interpretations of the CPB, or that simply carry out research. Minimising the number of new regulatory data requirements and maximising the value of existing studies will reduce development and opportunity costs, and thereby increase the prospects for *Bt* crops, and transgenic insect-resistant crops in general, to improve food security in developing countries.

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Alan Raybould is a Science and Technology Fellow at Syngenta where he works in the Product Safety department. He has extensive experience of conducting regulatory risk assessments for transgenic maize and cotton producing insecticidal proteins. In his work for Syngenta, and for industry organizations such as CropLife International, he has participated in efforts to develop effective environmental risk assessment methods for transgenic crops through seminars and workshops in many countries. Before joining Syngenta, Dr Raybould was a research scientist at the UK's Centre for Ecology and Hydrology where he worked on predicting the effects of pest-resistance transgenes in wild relatives of crops.

Hector Quemada is the Director of the Biosafety Resource Network at the Donald Danforth Plant Science Center. This project provides regulatory expertise in support of crop development projects funded by the Bill and Melinda Gates Foundation. He is also the manager of the Biotechnology and Biodiversity Interface grant program, a component of the Program for Biosafety Systems, led by the International Food Policy Research Institute and funded by the United States Agency for International Development. For eleven years, he was the founder and principal consultant for Crop Technology Consulting, Inc., an agricultural biotechnology consulting firm offering services in technical assessment, product development, project management, and regulatory affairs. Dr. Quemada has conducted biotechnology risk assessment research funded by the US Department of Agriculture, and under contract to private companies. Dr. Quemada's consultancies have included technical and biosafety assessment for national biotechnology programs in India, the Philippines, Uganda, Kenya, South Africa, Egypt and Indonesia.