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ECONOMIC, ECOLOGICAL, FOOD SAFETY, AND SOCIAL CONSEQUENCES OF THE DEPLOYMENT OF BT TRANSGENIC PLANTS

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■ **Abstract** Transgenic plants expressing insecticidal proteins from the bacterium, *Bacillus thuringiensis* (Bt), are revolutionizing agriculture. Bt, which had limited use as a foliar insecticide, has become a major insecticide because genes that produce Bt toxins have been engineered into major crops grown on 11.4 million ha worldwide in 2000. Based on the data collected to date, generally these crops have shown positive economic benefits to growers and reduced the use of other insecticides. The potential ecological and human health consequences of Bt plants, including effects on nontarget organisms, food safety, and the development of resistant insect populations, are being compared for Bt plants and alternative insect management strategies. Scientists do not have full knowledge of the risks and benefits of any insect management strategies. Bt plants were deployed with the expectation that the risks would be lower than current or alternative technologies and that the benefits would be greater. Based on the data to date, these expectations seem valid.

CONTENTS

PERSPECTIVES AND OVERVIEW 846
Bt CROPS AND THEIR TARGETED INSECTS 848
Bacillus thuringiensis 848
Commercialized Bt Crops 848
Bt Crops under Development 850
INFLUENCE OF Bt PLANTS ON INSECTICIDES USED AND THE ECONOMICS OF PRODUCTION 851
Cotton 851
Corn (Maize) 853
Potatoes 855
Overall Conclusions 856
INFLUENCE OF Bt PLANTS ON THE ENVIRONMENT, NONTARGET ORGANISMS, AND OTHER CROPS 856

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Outcrossing 857
Bt Plants Becoming Weeds 857
Horizontal Transfer 858
Soil Organisms 858
Other Nontarget Organisms 859
Summary 861
RESISTANCE MANAGEMENT CONSIDERATIONS 862
Overall Conclusion 864
REGULATORY AGENCIES FOR Bt PLANTS 864
United States 864
China 865
Australia 866
RISK ANALYSIS 866
FOOD SAFETY 867
THE SOCIAL ISSUES 870
Consolidation of Agriculture 870
Trade Issues and the Global Food Supply 871
Labeling 872
Ethics 872
THE FUTURE 873

PERSPECTIVES AND OVERVIEW

A Chinese saying, often regarded as a curse, is "May you live in interesting times," and perhaps there are no more interesting times in agriculture than the present. Biotechnology is allowing agricultural crops, as well as many nonagricultural products such as medicines, to be altered in ways that were not thought possible even by those who led the Green Revolution only four decades ago. Agriculture is going through another revolution, but this time it is part of the larger revolution in genetics, which has been proclaimed as the third technological revolution following the industrial and computer revolutions (3). Technical aspects of agricultural biotechnology have been rapid, but their deployment and impact have been controversial. Daily news events on the scientific and social implications of agricultural biotechnology describe an ever-evolving story, one that evokes considerable passion in public and scientific meetings. In this article we analyze and critique some of the most important issues surrounding agricultural biotechnology, especially as related to *Bacillus thuringiensis* (Bt) plants.

The revolution in agriculture has two parts: genomics, which seeks to understand (and modify) the organization of traits within the chromosomes of a species, and transgenics, in which the traits of an organism are changed by transferring individual genes from one species to another. It is the latter that has attracted most of the public controversy. Plants have been genetically modified (GM) throughout the history of agriculture, but the present technology of moving individual genes through biotechnology is more appropriately called genetic engineering

(GE). Plants have been engineered to resist attack from insects and diseases, to be tolerant to herbicides, or to have longer shelf life. Additionally, plants are being engineered for such novel uses as remediation of metal-contaminated soils, vaccine production, or nutrient supplements (100). The promises of transgenic crops are profound: pest resistance, tolerance to other biotic and abiotic stresses, healthier food, and more environmentally compatible production practices. Although there have been great strides in the development of new technologies that can be used in agriculture, the suite of currently available biotechnology products are actually few. We are in the first generation of such products and most of these have been used for pest control. Still on a worldwide basis, the adoption rates for transgenic crops have been unprecedented in agriculture (73).

It is expected that the world market for GE plants will be $8 billion in 2005, and $25 billion by 2010 (72). The number of countries growing transgenic crops commercially has increased from 1 in 1992 to 13 in 1999. Between 1996 and 2000, the global area of transgenic crops increased by more than 25-fold, from 1.7 million ha in 1996 to 44.2 million ha in 2000 (73). Three of the countries (United States, Canada, and Argentina) grew 98% of the total. The countries with commercial GE crop production (and percentage of the total global transgenic crops) in 1999 were: United States, 30.3 million ha (68%); Argentina, 10.0 million ha (23%); Canada, 3.0 million ha (7%); China, 0.5 million (1%); and Australia and South Africa, each with less than 0.2 million ha (<0.5%) (73). Adoption of this new technology, like most other technologies, has been fastest in the industrialized countries, but the proportion of transgenic crops grown in developing countries has increased consistently from 14% in 1997, to 16% in 1998, to 18% in 1999, and to 24% in 2000.

Within this overall context of transgenic plants, herbicide tolerance is the most common trait and constituted 74% of all transgenic crops in 2000 (73). According to James (73) on a worldwide basis in 2000, Bt corn was grown on 6.8 million ha (15% of total transgenic crops) with an additional 1.4 million ha (3% of total transgenic crops) planted to Bt/herbicide-tolerant corn. Bt cotton was grown on 1.5 million ha (3% of total transgenic crops) with an additional 1.7 million ha (3% of total transgenic crops) grown to Bt/herbicide-resistant cotton. Bt potatoes were grown on <0.1 million ha (<1% of the total transgenic crops).

In 1995, the U.S. Environmental Protection Agency (EPA) approved the first registration of Bt corn, potato, and cotton products; now more Bt crops are grown in the United States than in any other country. The use of Bt corn and Bt cotton has increased dramatically in the United States (146). The percentage of total area of Bt corn in the United States was <1% (0.16 million ha) in 1996, but 6% (1.78 million) in 1997, 18% (5.87 million) in 1998, and approximately 26% (8 million) in 1999, 2000, and 2001. The area of Bt cotton in the United States increased from 0.73 million ha in 1996 to 0.84 million in 1997 and 1 million in 1998. In 2000, 1.78 ha of the cotton was Bt cotton (25). The area grown in potatoes has never exceeded approximately 20,000 ha (<4% of the overall potato production) and is now in decline (see below).

Bt CROPS AND THEIR TARGETED INSECTS

Bacillus thuringiensis

Bt is an aerobic, motile, gram-positive, endospore-forming bacillus initially isolated in Japan by Ishiwata and formally described by Berliner in 1915 (129). The insecticidal activity of Bt used commercially thus far comes from endotoxins included in crystals formed during sporulation, although "vegetative insecticidal proteins" (Vips) from before sporulation (159) are also being developed. The crystals of different strains of most Bts contain varying combinations of insecticidal crystal proteins (ICPs), and different ICPs are toxic to different groups of insects. More than 100 Bt toxin genes have been cloned and sequenced, providing an array of proteins that can be expressed in plants or in foliar applications of Bt products (54). Insecticidal products containing subspecies of the bacterium *B. thuringiensis* were first commercialized in France in the late 1930s with the product Sporeine. In 1995, there were 182 Bt products registered by EPA, but even in 1999 the total sales of Bt products constituted <2% of the total value of all insecticides.

Commercialized Bt Crops

Bt was first introduced into tobacco plants in 1987 (150). However, much more effective plants that used synthetic genes modeled on those from Bt but designed to be more compatible with plant expression (26, 79, 111, 112) were introduced a few years later. Of the $US 8.1 billion spent annually on all insecticides worldwide, it has been estimated that nearly $2.7 billion could be substituted with Bt biotechnology products (80). Insects targeted for control by Bt plants are primarily Lepidoptera through the production of Cry1Ab, Cry1Ac, and Cry9C proteins, although one product has been developed for control of the Colorado potato beetle, *Leptinotarsa decemlineata*, using Cry3A.

CORN Monsanto markets Bt corn as MON810 and under different names (Table 1). MON810 represents >85% of the Bt corn planted worldwide. Syngenta Seeds (formerly Novartis Seeds) currently has two Bt corn events known in the regulatory arena as Event 176 and Bt11. The trade name for Event 176 is "Knockout®", whereas Bt11 is sold as NK-brand Bt corn with YIELDGARD (a trademark of Monsanto company), both of which contain the *cry1Ab* gene. Event 176 and Bt11 are approved in many countries. Bt11 is another dominant Bt corn variety, while Event 176 constituted <2% of the total corn grown in the United States in 1999 (65b).

Aventis marketed StarLink corn, which contains Cry9C protein and is approved only for animal feed and ethanol production. Its registration was voluntarily cancelled in the United States in October 2000 because of its inadvertant introduction into human food supplies.

Within the European Union some individual countries, in defiance of the EU approvals (see below), have enacted bans against imports of specific crops. Examples

TABLE 1 Bt crops currently registered, by country and date, for production,[a] as of July 2001

Crop/Company	Event	Country	Year of approval
YieldGard® Corn/Monsanto	MON810	Argentina	1998
	MON810	Bulgaria	2000
	MON810	Canada	1997
	MON810	EU	1998
	MON810	South Africa	1999
	MON810	USA	1996
NK Brand Bt Corn with YieldGard® /Syngenta	Bt11	Canada	1996
	Bt11	USA	1996
Knockout® Corn/Syngenta	Event 176	Argentina	1998
	Event 176	Canada	1996
	Event 176	EU	2001
	Event 176	USA	1995
Bollgard® Cotton/Monsanto	531	Argentina	1998
	531	Australia	1996
	531	China, Hebei[b]	1997
	531	Indonesia	2001
	531	Mexico[c]	1996
	531	South Africa	1997
	531	USA	1995
Bt Cotton/CAAS[d]	GK	China	1997
Bt Cotton/CAAS[d]	sGK	China	1999
New Leaf Potato[e]/Monsanto	Russet Burbank, Atlantic, Superior	USA	1995
	Russet Burbank	Canada	1995
	Russet Burbank, Superior	Romania	1999
New Leaf Plus/Monsanto	Russet Burbank 350, 129	USA	1998
New Leaf Y/Monsanto	Russet Burbank, Shepody	USA	1999
	Russet Burbank, Shepody	Canada	1999

[a]Registration means crops can be grown and harvested. These registrations do not necessarily include approval for import or food production in the country.

[b]Hebei was the first province to approve Bollgard cotton in China; subsequently, there have been approvals in Anhui and Shandong provinces.

[c]Annual approval for scale of production.

[d]Chinese Academy of Agricultural Sciences.

[e]Approval dates apply to the first varietal approval; additional approved varieties are covered by separate approvals.

include the ban on Event 176 imposed by Luxembourg and Austria. Austria also banned MON810. Italy banned all GM corn under the EU novel food regulation, which includes Bt11, MON810, MON809, and T25. There are no domestic restrictions on the use of grain or fodder from either Event 176 or Bt11.

COTTON Monsanto markets Cry1Ac cotton, Event 531, under different trade names in several countries (Table 1). There were three Bt cotton Events in 1999 in China, one from Monsanto and two developed in China. Event "GK" has a modified *cry1A* gene (62), and "sGK" has two insecticidal genes, *cry1A* and *CpTI* (cowpea trypsin inhibitor) (63). Other stacked *cry1Ac* and *cry2Ab* Bt products for insect control in cotton are being developed (61) because models have shown advantages of such pyramided varieties for insecticide-resistance management (118).

POTATO A Monsanto-affiliated company, NatureMark, marketed Cry3A potatoes in the United States, Romania, and Canada under variations of the trade name, NewLeaf. However, in 2001 the company stopped marketing Bt potatoes.

Bt Crops under Development

Rice is grown on >145 million ha and provides 20% of the per capita energy and 15% of the per capita protein for humans worldwide. More than 90% of the area planted to rice lies in Asia (116). Among the primary pests of rice are Lepidoptera, particularly the yellow stem borer, *Scirpophaga incertulas*; the striped stem borer, *Chilo suppressalis*; and leaffolders such as *Cnaphalocrocis medinalis*. Breeders have not produced rice with high levels of resistance to these pests through conventional means, so the development of Bt rice creates options for control. Several laboratories around the world have transformed rice with Bt genes and evaluated them in greenhouse and field trials (140, 157), but no Bt rice varieties have been released to farmers (34).

Efforts are under way to commercialize corn with a *cry3Bb* gene or a binary toxin genetic system for control of the corn rootworm (*Diabrotica*) complex (60). The *Diabrotica* complex occurs primarily in North America and is a major target of insecticides in the United States with losses and control costs estimated at $1 billion annually (87). At least one company (Monsanto) hopes to sell Bt corn for rootworm control in the United States in 2002. Genes expressing toxins for European corn borer (ECB) and the corn rootworm complex are expected to be stacked in plants. Resistance management strategies, developed through models, are being evaluated to help guide EPA policies.

Other Bt crops under development are canola/rapeseed, tobacco, tomato (80), apples, soybeans, and peanuts. Broccoli and cabbage have been transformed to express Bt ICPs for control of the diamondback moth (DBM), *Plutella xylostella*, but these crops have been used primarily to evaluate resistance management strategies (125), although companies are evaluating the potential for commercialization. Great care must be taken to develop such plants because DBMs have already developed high levels of resistance in some areas to foliar applications of Bt products containing Cry1A and Cry1C toxins (125, 136). Potatoes have also been successfully transformed to express Cry1Ab and Cry5 toxins for control of the potato tuber moth, *Phthorimaea operculella* (39, 74, 89).

INFLUENCE OF Bt PLANTS ON INSECTICIDES USED AND THE ECONOMICS OF PRODUCTION

Cotton

On a worldwide basis, cotton is grown on >32 million ha with approximately 71% of the production in developing countries (50). The major production countries (and their percentages of the total production) are India (28%), United States (16%), and China (10%). Cotton receives the most insecticide use of any crop worldwide.

Cotton is attacked by a complex of insects including plant bugs, aphids, whiteflies, and the boll weevil; however, on a worldwide basis, the main pests are the diverse set of Lepidoptera that feed on the cotton buds or bolls (84) and against which most of the insecticides are targeted. In the United States, the primary target pests in cotton are the tobacco budworm *Heliothis virescens* and cotton bollworm *Helicoverpa zea* (84). Insecticides against the lepidopteran complex are used on at least 75% of the cotton acreage (25). The pink bollworm, *Pectinophora gossypiella*, is found throughout much of the cotton-producing areas of the world but is restricted to Texas westward in the United States (27). Throughout the Americas, *H. zea* and *H. virescens* must be controlled annually on much of the cotton areas, but there are difficulties with control because *H. virescens* is resistant to many organophosphate and pyrethroid insecticides and damage even in the presence of insecticides can be significant (84). Throughout the rest of the world, *Helicoverpa armigera* is a primary pest (84) with resistance levels and crop losses comparable to *H. virescens* (158).

In the United States there are two surveys conducted annually on pesticides used in cotton. The USDA National Agricultural Statistics Service (NASS) reports on area treated and amount of insecticide used per state. The second survey, coordinated through the Cotton Foundation and published in the Beltwide Cotton Conference Proceedings, relies on information provided by the public and private sectors involved in cotton production in producing states. Using these sources, the National Center for Food and Agricultural Policy (NCFAP) conducted an analysis of the influence of Bt cotton on insecticide-use patterns (25, 57). The authors noted the difficulty in conducting their analysis because different pest complexes occurred across the cotton-producing regions, the severity of infestation varied across regions, suitable cotton varieties with Bt were not available for all regions, levels of resistance to foliar insecticides varied across regions, and the effectiveness of Bt varied according to the individual pest species. With these caveats, insecticide use was compared for 1995, the year before Bt cotton varieties were introduced, and for 1998 and 1999, with adjustments for differences in area planted for these two years. Using data from six states, the results indicate that there was an overall reduction in use of insecticides for the bollworm/budworm complex and pink bollworm of >2 million lbs in 1998 and 2.7 million lbs in 1999. The number of insecticide applications also declined by 8.7 million in 1998 and 15 million in 1999, or 13% and 22% of the total number of insecticide applications in 1995. The authors noted that some of this reduction may have been due to other factors, such as the simultaneous boll weevil eradication programs that allowed beneficial insects to increase and control the Lepidoptera. On the other hand, they also noted that because Bt controls only Lepidoptera, secondary pests such as tarnished plant bugs and stink bugs may have increased and insecticides may have been targeted against them in Bt cotton fields.

The U.S. EPA has also compiled its own analysis of the effect of Bt cotton on insecticide-use patterns (146). Using data from NASS, the EPA noted reductions in insecticide use are highest in the Deep South, in states such as Alabama where it is predicted that "two to eight or more insecticide applications targeted for bollworms and budworms" may be replaced by Bt cotton. Using data from NASS, EPA conducted an analysis of "high-adopter states" (>60% of cotton planted to Bt cotton) (Arizona, Louisiana, and Mississippi) and "low-adopter states" (<20% of cotton planted to Bt cotton) (Arkansas, Texas, and California), and their analysis indicates a "significant reduction in treatments per acre" in the high-adopter states. They estimate the reduction to be from 3 to 1.5 treatments per acre for control of Lepidoptera but noted the increased need to control secondary pests drops the overall insecticide reduction to 1.2 treatments per acre. In the low-adopter states, a use-reduction estimate could not be calculated. Based on the 1.2 spray savings figure, EPA (146) estimates that in 1999 there was a 7.5-million-acre treatment reduction when the figure is applied to the 13.3 million acres planted in 1999.

Both NCFAP and EPA used the same insecticide data (NASS) and calculated active-ingredient acre treatments (an application acre is the number of different active ingredients applied per acre times the number of repeat applications). Although both calculated large reductions in insecticide use due to Bt cotton, their estimates are different for 1999 data and are owing to EPA's use of data from three high-adopting states to obtain their figure of an overall reduction of 1.2 treatments per acre and then using that figure across the other high-adopter states. NCFAP observed changes in total application across six states.

An analysis by Williams (151) of insecticide use in six states for control of the lepidopteran complex also indicates substantial reductions owing to the use of Bt cotton. In 1995, prior to the introduction of Bt cotton, the number of insecticide treatments ranged from 2.9 (Arizona) to 6.7 (Alabama) and averaged 4.8. By 1998, the range varied from 3.5 (Louisiana) to 0.4 (Arizona) and averaged 1.9, an overall reduction of 60%. The use of Bt cotton in Arizona for pink bollworm in 1997 eliminated 5.4 insecticide applications and saved growers $80 per acre (27).

Economic analyses using several different methods show a consistent positive economic return to U.S. growers when they use Bt cotton (146). These economic benefits to growers on a national level vary from year to year and from model to model, but range from 16.3 to $161.3 million. Carpenter & Gianessi (25) stated that Bt cotton farmers in 5 studies in 7 states had a 9% yield increase with Bt cotton and that these yield and revenue impacts, if realized over all 4.6 million acres of Bt cotton in 1999, would result in a $99 million increase in revenue. Frisvold et al. (53) provided a more regional-based analysis and estimated that benefits to Bt adopters grew from $57 million in 1996 to $97 million in 1998. In an economic analysis of the distribution of the economic benefits of Bt cotton, Falck-Zepeda et al. (45) calculated that the introduction of Bt cotton created an additional wealth of $240.3 million for 1996. Of this total, the largest share (59%) went to U.S. farmers. Monsanto, the developer of the technology, received the next-largest share (21%), followed by U.S. consumers (9%), the rest of the world (6%), and the seed companies (5%).

In China, Bt cotton plants have provided a 60–80% decrease in the use of foliar insecticides (156). The economic benefits of Bt cotton to growers in Liangshan county of Shandong province were $930/ha in 1998, and the estimated average benefits were about $250/ha in 1998–2000 (75). In a larger survey of 283 cotton farmers in Northern China in 1999, Pray et al. (114) reported the cost of cotton production for small farmers was reduced by “20 to 33 percent depending on the variety and location” by using Bt cotton, and “the net income and returns to labor of all the Bt varieties are superior to the non-Bt varieties.” This study also estimated a reduction of 15,000 tons of pesticide. In Australia from 1996 to 2000, Bt cotton has reduced insecticide use for bollworms by 4.1 to 5.4 sprays (43–57%) per year, with an overall reduction of all sprays from 37 to 52% (32, 33, 81, 82). Due to the technology fee for the seed, Australian growers are saving little on costs but are keen to adopt Bt cotton for the improved certainty of yields and to reduce concerns about environmental contamination with insecticides (52). The reductions in China and Australia (32) may be lower than in the United States because *Helicoverpa* species, which are the main pests there, are at least tenfold less sensitive to Cry1A than *H. virescens* (134), the key pest in the United States. In Mexico the use of Bt cotton allowed growers to save 55,090 liters of foliar insecticides and 4613 pesos/ha (90).

Corn (Maize)

Hybrid field corn, open-pollinated flint corn, popcorn, and sweet corn are grown on every populated continent. In 2000 corn was grown on >138 million ha, with the majority grown as field corn (50). Developing countries (according to World Bank classifications) grow approximately 70% of the world’s corn. Global maize production totaled 579 metric tons in 1996, with 67% going for animal feed (31, 50). The major foliar pests of corn worldwide are the ECB, *Ostrinia nubilalis*; Asiatic corn borer (ACB), *Ostrinia funicalis*; southwestern corn borer (SWCB), *Diatraea grandilosella*; corn earworm (CEW), *H. zea*; fall armyworm (FAW), *Spodoptera frugiperda*; and black cutworm (BCW), *Agrotis ipsilon*. ECB, considered the major pest of corn worldwide, damages corn by tunneling into stalks causing lodging and reduced flow of nutrients, resulting in overall yield reductions. Infestations by Lepidoptera in the ear may result in increased production of mycotoxins associated with a variety of adverse health effects in livestock and are suspected of causing cancer (91, 137). In the United States and Canada, ECB is the most damaging lepidopteran insect and losses resulting from its damage and control costs exceed $1 billion yearly. In a four-year study in Iowa, the combined losses due to first- and second-generation borers were 25 bushels per acre (108).

ECB populations vary considerably by region and by year, and management practices are tailored accordingly (86). However, on a national scale "more farmers ignored ECB than treat it with insecticides" despite many studies indicating that well-timed sprays can produce high levels of control and significantly increase yield (25). NCFAP reports that approximately 1.5 million lbs of active ingredient were used to control ECB in 1996, nearly 60% of which was the organophosphate insecticide chloropyrifos (57). In 1997, 7.1% (5.9 million acres) of the total corn planting in the United States was treated with insecticides for ECB; in the southern west region (Arkansas, Louisiana, Mississippi, Texas, and Oklahoma) nearly 25.2% of the corn area was treated.

Because most growers do not presently use insecticides to control ECB but accept the losses it causes, it is difficult to assess the impact of Bt corn. However, 30% of the growers who planted Bt corn in 1997 indicated they did so to eliminate the use of foliar insecticides for control of ECB (25). Growers' buying habits seem to validate these statements because the percentage of Bt corn in the total crop has grown from <1% in 1996 to 26% in 2001. Because some growers used insecticides to control ECB prior to the introduction of Bt corn, there has been a decrease in use due to Bt corn. Comparing 1995, the year before Bt corn was introduced, to 1999, the use of five recommended insecticides for control of ECB declined. Carpenter & Gianessi (25) concluded that a 1.5% decline in their use was due to Bt corn, amounting to approximately 1 million acres not sprayed for ECB control. A survey of Bt corn producers ($n = 7265$) from six states (Illinois, Iowa, Kansas, Minnesota, Nebraska, and Pennsylvania) after each of the first three growing seasons when Bt corn was available for commercial production documents that insecticide use for ECB is declining. The percentage of Bt corn producers that used less insecticide for this pest nearly doubled from 13.2 to 26.0% during the 3-year period (65a). The SWCB occurs in several central states of the United States where it can cause "devastating losses" of more than 70 bu per acre (149), but it has effectively been controlled by Bt11 and MON810 (20).

EPA also did an analysis of the impact of Bt corn in six states for which annual insecticide use on corn were available for 1991–1999. The states were divided into high adopters (>25% of corn is Bt) (Iowa, Illinois, Nebraska, Missouri) and low adopters (<10% of corn is Bt) (Indiana and Wisconsin). In the high-adoption states, there was a "reduction from 6.0 million to slightly over 4 million acre treatments in 1999, a reduction of about one-third" (146). No such decline was observed for low-adopter states.

The EPA (146) noted that through extensive research and modeling studies, the overall conclusion was that "ECBs cause significant yield loss but infestation levels and resulting loss are inconsistent from year to year, and therefore, it is difficult to predict whether control is needed. The premium paid for Bt-corn seed will likely only be returned in years when corn borer infestations are moderate to heavy (and) declining corn prices to sub-$2.00/bushel levels since 1998 along with low pest pressure have reduced the (economic) benefits of Bt-corn." The NCFAP study (25) estimates an average net benefit to growers of $18 per acre in 1997 (a year of high infestation) to a loss of $1.81 per acre in 1998 (a year of low infestation and corn prices). The EPA estimates, using another model, indicate a net benefit of $3.31 per acre on 19.7 million acres of Bt corn planted in 1999, or a national benefit of $65.4 million (146). Carpenter & Gianessi (25) estimate that in "10 of the 13 years between 1986 and 1998, ECB infestations were such that corn growers would have realized a gain from planting Bt corn."

Sweet corn has also been modified to express Cry1Ab toxins from the Bt11 event, and EPA approved the registration of Novartis' product in 1998. The major market for sweet corn worldwide is the United States, where >700,000 acres are grown (141). The main insects attacking sweet corn include ECB as well as CEW and FAW, but the main species and its abundance change according to region. Conventional control tactics vary not only according to the pest species and region, but also according to the market requirements (fresh versus processing). Nationally nearly 3.2 million acre treatments are applied annually for control of insects affecting sweet corn (141), for an average of 4.3 treatments for processed corn and 8.6 for fresh market. In Florida, foliar applications of insecticides may be applied up to 16.9 times per crop (141, 146). Because of the higher expression of Bt proteins in sweet corn compared with field corn, good control of CEW and FAW occurs in sweet corn even though there is considerable survival of the same pests on field corn. EPA estimates that there were 30,000 acres of Bt sweet corn planted in 1999. With a savings of 4.3 treatments per crop, EPA estimates the total-use reduction was 127,000 acre treatments in 1999 (146). EPA's simulation model for sweet corn (146) indicates "an average net benefit per acre of $3.55 for processing corn and $5.75 for fresh corn" in 1999.

Potatoes

Worldwide, potatoes were grown on >18.7 million ha. in 2000 (50). Unlike cotton and corn, the majority of potato area (56%) is in developed countries. However, China has the largest area under potato production (20%), followed by Russia (17%). The Colorado potato beetle is the most destructive chewing-insect pest of potatoes on a worldwide basis and occurs in most parts of the United States and has spread to Asia and Europe. This beetle is noted for its ability to evolve resistance to insecticides (28). Currently in the United States, only Monsanto's New Leaf varieties, which express Cry3A, are registered after being approved in 1995. Limited production of Bt potatoes has occurred because of market concerns for GE foods and because a foliar insecticide, imidacloprid, was introduced as an effective alternative to Bt potatoes. Carpenter & Gianessi (25) indicate that 34% of the potato acreage was treated with imidacloprid in 1999. The total U.S. area planted to Bt potatoes has never exceeded 50,000 acres, or 4% of the market.

In the United States 34% of the total insecticide use on potatoes is for control of CPB (25). About 80% of the current insecticide use on potatoes comes from organophosphates and pyrethroids. According to a survey of growers in 1998 (25), those who used Bt potatoes applied 1.35 fewer insecticide applications and the Bt potatoes required 0.48 lbs less active ingredients of insecticides. Based on the estimated 4% of the market share for Bt potatoes, EPA (146) estimates that the benefit to growers is $9.30 per acre or $500,000 nationally and results in 89,000 fewer acre treatments.

Overall Conclusions

EPA's analysis of economic return and insecticide reductions for registered Bt crops in the United States in 1999 (146) are estimates derived from the percent of the total area of a specific crop that is planted with a Bt variety. Results indicate an overall economic benefit to growers of $65.4 million (field corn), $45.9 million (cotton), $0.2 million (sweet corn), and $0.5 million (potatoes), for a total economic benefit of $111.9 million. EPA's analysis also indicates a reduction of 7.5 million fewer acre treatments (cotton), 0.127 million (sweet corn), and 0.089 million (potatoes), but it did not calculate a figure for field corn because of variable insect pressure. Other studies have documented declines in insecticide use in field corn (25, 65a).

In contrast to the figures reported by EPA and NCFAP, Wolfenbarger & Phifer (152) provided an overview of GE crops and pesticide-use patterns. Although their report did not break out insecticide-use patterns in as much detail as EPA or NCFAP, they questioned some of the assumptions used by NCFAP in the corn insecticide analysis, yet did not provide an alternative. Subsequently, in a letter to the editor, Carpenter (24) stated that Wolfenbarger & Phifer's article did not cite analyses of changing insecticide-use patterns on cotton, which Carpenter indicates as "the crop for which the most dramatic reductions in pesticide use have been observed." In reply, Wolfenbarger & Phifer (153) questioned whether substituting one insecticide (Bt) for another (a broad-spectrum foliar insecticide) is really a reduction. Clearly, the authors have different perspectives on how to measure insecticide reductions and their ecological impacts.

INFLUENCE OF Bt PLANTS ON THE ENVIRONMENT, NONTARGET ORGANISMS, AND OTHER CROPS

Reductions in the use of broad-spectrum insecticides would likely result in conservation of natural enemies and nontarget organisms, decreased potential of soil and water contamination, and benefits to farmworkers and others likely to come into contact with these insecticides (94). In a survey of 283 cotton farmers in China, Pray et al. (114) reported that farmers "using Bt cotton reported less pesticide poisonings than those using conventional cotton." A more complete assessment of the environmental impact of Bt plants would include the fate of Bt proteins in the environment, their direct and indirect impact on natural enemies and nontarget organisms, the frequency with which pollen from Bt plants fertilizes other plants, and horizontal gene transfer in which the plant genes may move into other organisms. EPA, as the agency charged with regulating the use of Bt plants in the United States, has served as the clearinghouse for studies examining these various aspects. Additional synthesis studies have been published by Snow & Palma (131), Traynor & Westwood (139), and Wolfenbarger & Phifer (152). The National Research Council's Standing Committee on Biotechnology, Food and Fiber Production and the Environment sponsored a workshop in July 2000 on ecological monitoring of GE plants to discuss what is known and what needs to be done (95).

Outcrossing

In the case of those plants registered in the United States (corn, cotton, and potatoes), EPA reviewed the potential for gene capture and expression of Bt endotoxins by wild or weedy relatives of these three crops and concluded that there is "not a reasonable possibility" of passing their traits to wild relatives because of differences in chromosome number, phenology, and habitat (146). The only exception is cotton in Florida and Hawaii, where feral populations exist of related *Gossypium* species, and EPA has prohibited or restricted the use of cotton in these areas. The situation in areas in the centers of origin is far more complex. For example, in Mexico there are several subspecies of teosinte, the wild relative of maize. Gene flow from teosinte to maize is well established (105), and it is also possible for genes to flow from maize to teosinte (38). In fact, the generally higher amount of pollen in commercial crops indicates a higher likelihood of pollen moving from a commercial maize crop into teosinte. Similar concerns about growing transgenic plants within an area containing wild relatives need to be addressed for other crops, and efforts are being made to engineer plants to reduce the likelihood of outcrossing. Because transgenic seeds may be moved by man and other organisms much more readily than in the past, regulations should be enforced to insure that seeds from transgenic plants are not grown in areas where they may develop into plants that can outcross with wild or weedy relatives.

Bt Plants Becoming Weeds

Crawley and coworkers (37) reported results of a 10-year study carried out in three locations in Britain that investigated whether GE crops, including Bt plants, could become weeds of agriculture or invasive to natural habitats. They evaluated rape, corn, and sugar beet resistant to herbicides and potato expressing Bt. These GE plants were planted in plots mixed with versions of the same species but bred through traditional breeding methods. They concluded that, "In no case were the GM plants found to be more invasive or more persistent than their conventional counterparts." Although these results do not demonstrate that all GE plants are safe in all circumstances, they do indicate that, at least for the crops tested, including Bt potatoes, the ability of a GE crop to become dominant-invasive plants in the wild is limited. However, larger-scale studies are needed to expand the database.

Horizontal Transfer

Because *cry* genes originate from soil bacteria, it is important to evaluate the potential for gene transfer from GE plants to other organisms, primarily bacteria, as well as soil organisms (see below). Crop residue, pollen, or root exudates may be potential sources of DNA in the soil. Available data indicate the half-life of Cry proteins incorporated into the soil in corn plants, the most extensively studied, is 1.6–22 days but can be as long as 46 days, although the amounts will be small (146). These numbers vary considerably based on soil characteristics. DNA from crop plants can remain in the soil from several months to several years (56, 109) if protected from soil nucleases, but the amounts are small (146). Additionally, even with much higher concentrations of DNA, "transformation of bacteria with plant transgenes has only been accomplished at low frequencies and under optimum conditions," and therefore "DNA transfer occurs rarely if at all from plants to bacteria" (146). Others (104) noted that other nonhomologous transgenes could, in theory, be transferred using the homology of bacterial sequences in transgenic plants but this would be rare, if it occurred at all.

Soil Organisms

Exposure to soil microorganisms and invertebrates can result from crop residues as well as from the roots themselves during and after the growing season. Whereas most of the concern of Bt plants has focused on crop residues, actively growing plants can increase the level of Cry1Ab in the soil. Stotsky and coworkers (120) found Cry1Ab protein in the exudates of 13 Bt corn hybrids, representing three transformation events (Bt11, MON810, and 176). They note that the toxin could accumulate in the soil during plant growth as well as crop residues. To assess the effects of Cry1Ab toxin released in the root and from biomass on soil organisms, they introduced earthworms into soil grown to Bt and non-Bt corn or amended with biomass of Bt or non-Bt corn. Although the protein was present in the casts and guts of worms in the Bt treatments, there were no significant differences in mortality or weight of the earthworms, nor in the "total numbers of nematodes and culturable protozoa, bacteria (including actinomycetes), and fungi between rhizosphere soil of Bt and non-Bt corn or between soils amended with Bt or non-Bt biomass" (121).

In another report (44), foliage of Cry1Ab corn was compared with foliage of the corresponding nontransgenic maize variety in laboratory feeding experiments to study the effects of the Bt protein on the decomposer *Porcellio scaber* and on leaf litter–colonizing microorganisms. Overall, the authors concluded they could not detect significant differences in populations of this single decomposer.

EPA (146) concluded the findings to date indicate that Bt soils "show no effect of total biomass, bacteria, actinomyces, fungi, protozoa or nematodes . . . (and) the C/N ratio is not changed . . . ." Their analysis also indicates the same persistence of Bt proteins in the soil from repeated Bt sprays as when Bt crops are grown. The EPA report concluded by noting that "sufficient data exist to suggest that adverse effects of currently commercialized Bt Cry1Ab and Cry1Ac proteins in the soil are not likely, although the levels of expression in the root, where not currently available, should be determined to assure that unexpectedly high levels of root expression are not found." They also noted that the levels of root expression of Cry9C are below those used in toxicity tests that have shown no adverse effects, but EPA does suggest further testing of Cry3A.

Although the data to date do not indicate striking problems with Bt proteins in the soil, they point out the difficulty in working in a complex soil system. Studies often focus on single organisms under specific environmental conditions and over an often short period of time. Under these conditions the power to test for differences is relatively low, and longer-term and more complex studies are needed to ensure the integrity of important soil organisms.

Other Nontarget Organisms

Prior to the registration of the first Bt crop in 1995 (Event 176 corn), EPA evaluated studies of potential effects of Bt endotoxins on a series of nontarget organisms including birds, fish, honey bees, ladybugs, parasitic wasps, lacewings, springtails, aquatic invertebrates, and earthworms (142). Organisms were chosen as indicators of potential adverse effects when these crops are used in the field. These studies consisted of published reports as well as company reports. An extensive collection of reports can be seen electronically (6). The focus of these studies was primarily on toxicity to the species tested because, unlike some synthetic insecticides that bioaccumulate, there are no data to suggest that Bt proteins do so. From their review of existing data, EPA concluded there were "no unreasonable adverse effects to humans, nontarget organisms, or to the environment. . . ." (142). At that time, EPA and scientists working in this area knew that endotoxins from *Btk* (*kurstaki*) were toxic to many Lepidoptera, both target and nontarget. Exposure to Bt proteins by lepidopterous larvae was considered primarily owing to ingestion of leaf tissue of Bt corn plants, and insects feeding on these plants would be considered pests. Another method of exposure to lepidopterous larvae would be through pollen deposits. Prior to registration of Bt corn, the amount of protein expressed in leaves, roots, and pollen was documented (142). Corn pollen is one of the heaviest wind-dispersed pollen grains, and a previous report (115) stated that corn pollen tends to have limited movement out of the field, a fact later confirmed by Wraight et al. (155). In its opinion in the section on endangered species, EPA stated, "Although corn pollen containing CryIA(b) δ-endotoxin can drift out of corn fields, such pollen, at relatively high dosages, was not toxic to the test species representative of organisms likely to be exposed to such pollen when corn plants containing the *cryIA*(*b*) gene are grown." Based on this reasoning the EPA granted the first registration of Bt corn in 1995.

Since registration, at least two reports of effects on nontarget organisms have received considerable attention. Reports indicating that consumption of corn pollen affects the development and mortality of lacewing larvae has created discussion focusing on the compatibility of Bt plants and biological control (66–68). Hilbeck et al. (66) reported increased mortality and prolonged development when lacewing larvae were reared on either ECB or *Spodoptera littoralis* that had ingested corn leaves expressing Cry1Ab. As noted by EPA (146), the "experimental design did not permit a distinction between a direct effect due to the Bt protein on the predator versus an indirect effect of consuming a sub-optimal diet consisting of sick or dying prey that had succumbed to the Bt protein." Hilbeck et al. (66) noted that ECB will be unlikely hosts for lacewing larvae in Bt fields because ECB "will almost completely be eradicated" by the Bt plants. Although Hilbeck et al. (66) state that "no conclusions can be drawn at this point as to how results from our laboratory trials might translate in the field," they recommend that such tritrophic effects be studied but concluded that Bt transgenic plants "are still more environmentally friendly than most if not all chemical insecticides." In the second study (67), the authors found that high concentrations of Cry1Ab (100 μg of Cry1Ab/ml of artificial diet) fed directly to lacewing larvae were toxic. Concern about the methods used was expressed by EPA (146) because the dose "is at least 30 times that found in most corn tissues in the field" and in the "field setting the lacewing larvae have a choice of other insects or eggs to feed on (so) field exposure will be intermittent, rather than continuous" as in the methods used. Furthermore, they note that ECB first instars "die soon after they start eating Bt corn tissue" and that any surviving larvae "would normally be within the corn plant most of their larval life and not be available for consumption by chrysopids." These studies show the difficulty in conducting laboratory studies on tritrophic interactions that have relevance in the field. Interactions in the laboratory, although dramatic, may not be realistic in the field. Likewise, testing only a single factor in the laboratory may not produce the subtle effects that may arise in the field.

A second case concerns the monarch butterfly, *Danus plexippus*. In a scientific correspondence, Losey et al. (83) reported that Bt corn pollen may be a hazard to monarch butterfly larvae. Their study consisted of depositing an unspecified amount of corn pollen from N4640 (a Bt hybrid producing Cry1Ab protein) onto milkweed leaves and placing three-day-old larvae on the plants, recording leaf consumption, larval survival, and final larval weight over a four-day period. The authors found lower survival of larvae feeding on leaves dusted with Bt pollen compared with leaves dusted with untransformed pollen or on control leaves with no pollen. They also found reduced consumption of leaves dusted with Bt or untransformed pollen compared with control leaves with no pollen. From these laboratory data, the authors developed a scenario in which they hypothesized that there could be "potentially profound implications for the conservation of monarch butterflies" (83) with the widespread use of Bt corn. Although this report was criticized for its inappropriate design, methodology, and interpretation (69), it had worldwide repercussions (124), and in December 1999, EPA issued a data call in notice to registrants of Bt corn. At the same time, a monarch working group was organized and conducted extensive field and laboratory research in 1999 and 2000 (65b). Although it had been previously reported that Event 176 (representing $<2\%$ of the total corn area in the United States) does express the Cry1Ab toxin at higher levels owing to a pollen-specific promoter (79), levels of this toxin in Bt11 (the event used by Losey et al.) are essentially nontoxic to monarch larvae. It is unclear why such mortality was seen, unless the high dose caused nonspecific toxicity or was the result of contaminated pollen (see below).

Hansen & Obrycki (64) found mortality of monarch larvae from Bt corn pollen, but the authors acknowledged large discrepancies between the toxin levels in pollen that they measured and those from replicated measurements accepted by EPA (146). This discrepancy is the result of them using pollen samples containing 43% plant debris. These debris caused significant mortality and reduced weight gain by $>80\%$ (126). These debris (mostly anther parts) are an artifact of the collection method and are unrelated to the Bt corn pollen that may fall on milkweed plants, the natural host of monarchs. Thus, the two published studies on monarchs had methodological problems that skewed their results and interpretation. However, these two reports have had tremendous implications about how science is conducted (78) and communicated (126).

In another study, Wraight et al. (155) did not find Bt corn pollen toxic to the black swallowtail butterfly under field conditions. As this Annual Review chapter is going to press, a series of detailed studies on the effects of Bt corn pollen on monarch butterfly populations in the field are being submitted for publication. According to M.K. Sears, one of the coordinators of this two-year international study, the reports indicate that the risk to monarchs under present field conditions is “negligible.”

Summary

Toxicological studies on key pests, their natural enemies, and nontarget organisms, as required by EPA, provide important information that can be used in longer-term community studies to assess the potentially more subtle impact of Bt technology. However, it is important to keep in mind that, regardless of whether one uses Bt plants, a biological control agent, a resistant plant, an insecticide, a cultivation technique, or any other method to control a pest, if the pest population is reduced there will be some impact on the overall biological community.

Most studies on environmental impact of Bt plants have been conducted on a small scale and over a relatively short period of time. Such studies provide some ecologically relevant information (131) but do have limitations because they have not been the long-term studies suggested by some. Such efforts are limited by funding as well as the interest in moving products into the market. The USDA is reported to spend 1% of its funds on risk assessment to biotechnology (131), although this amount has increased considerably in recent years. In addition to long-term research studies, it is also important to have consistent approaches to field studies and ones that have a high power of statistical certainty. An EPA Scientific Advisory Panel (SAP) met in December 1999 and recommended that "The Agency (EPA) should consider how the data will be used and establish acceptable level of statistical power. Based on these decisions, appropriate tests and sample sizes can be determined" (145). As noted by Marvier (85), the lack of power in ecological studies may cause misinterpretation of a hazard. The National Academy of Sciences in the United States is currently undertaking a more comprehensive study entitled, "Environmental Impacts Associated with Commercialization of Transgenic Plants: Issues and Approaches to Monitoring" (97).

RESISTANCE MANAGEMENT CONSIDERATIONS

Resistance management for Bt plants (58, 119) remains a serious concern. The evolution of resistance to the toxins produced by Bt plants depends on the genetic basis of resistance, the initial frequency of resistance alleles in the population, the competitiveness of resistant individuals in the field, and a resistance management strategy. In order to have an effective resistance management strategy using the high dose/refuge strategy (the only strategy currently available), the frequency of resistant alleles and the survival of individuals heterozygous for resistance must both be low (10, 71).

A key to resistance management in Bt plants is the use of a refuge to conserve susceptible alleles within the population, and the debate has focused on the size of the refuge needed or indeed whether refuges that are large enough can be economically acceptable to the users or sellers of Bt crops (125, 144, 146). The maximum benefits to crop production, farm profitability, and reduction of pesticide use may come from larger proportions of transgenic crops, but long-term enjoyment of these benefits may be feasible only by limiting the percentage of the crops that are transgenic. U.S. growers of Bt cotton must chose one of three structural refuge options for the 2001 growing season: 95:5 external-structured unsprayed refuge, 80:20 external-sprayed refuge, or 95:5 embedded refuge (147). Modeling studies (107), a greenhouse study (136), and a field study (125) have indicated that separate refuges are superior to seed mixtures for delaying resistance for insects that can move between plants in the larval stage. Care must be taken in managing the insect population within the refuge to insure that sufficient susceptible alleles will exist (125).

The frequency of resistance alleles prior to the introduction of the crop is one of the most important factors determining the long-term effectiveness of the specific protein in the crop, and there has been considerable variation in these estimates. Gould et al. (59), using single-pair matings to a known resistant strain, estimated the frequency of the major Bt resistance genes in *H. virescens* collected from four states in 1993 (prior to the widespread introduction of Bt cotton) to be 1.5×10^{-3}. More recently, Tabashnik et al. (135) have noted a resistance-allele frequency of as high as 0.13 for the pink bollworm. In contrast, Ahmad (4) could not find major genes for resistance at frequencies of 10^{-3} in either *P. xylostella* or *H. armigera* using single-family lines in an F_2 screen (see below). Despite the studies that estimate higher Bt-resistance-allele frequencies than anticipated, their effects in the field are unclear. For example, resistance-allele frequencies in pink bollworm populations in Arizona have not correlated with product performance and have not translated into increased frequency of resistant individuals in subsequent generations despite increased usage of Bt cotton.

Detecting shifts in the frequency of resistance genes should utilize an aggressive monitoring method to detect the onset of resistance before widespread crop failure occurs. In general, resistance monitoring plans should include a detailed strategy for all pests susceptible to the expressed Bt proteins regardless of whether the insects are listed on the label. Detailed programs have been developed for cotton in Arizona (27) and Australia (R.T. Roush, unpublished information). Considerable care needs to be taken to define the spatial scale of monitoring (19). Using stochastic and spatially explicit simulation models, Peck et al. (110) examined the spread of resistance on a regional basis for Bt cotton. Their model included the age structure of adults and larvae, plant-to-plant movement of larvae within a field, migration of adults among fields, plant type-genotype–specific selection, and developmental time of generations. Their findings indicated that spatial scale and temporal pattern of refuges had a strong effect on the development of resistance in *H. virescens*. The authors recommend that resistance management be conducted on a regional level and must include strong grower cooperation. We believe that grower compliance to a resistance management strategy is essential to delaying the development of resistance.

The F_2 screen (9) has great potential to detect rare recessive alleles at low frequencies ($<10^{-3}$), a key point in managing resistance. However, to detect a resistance-conferring allele at low frequencies, a large number of family lines must be collected and reared. At least 750 family lines must be screened to have a 95% probability of detecting a resistance allele at a frequency of 10^{-3} (8, 122). Although several trials of the F_2 screen have been completed, including three on ECB, one on DBM, and one on *H. armigera*, resistance-conferring alleles have not been found using this method (4, 8, 10, 11). There is a need to evaluate the precision and accuracy of the F_2 screen by using colonies with known frequencies of resistance alleles. One such study (J.-Z. Zhao & A.M. Shelton, unpublished data) used the F_2 screen with well-characterized strains of DBM. Results indicate that the F_2 screen can document low allele frequencies, but using the Bt plant as the screening method on the F_2 generation may underestimate the frequency of resistance alleles. Thus, procedures used in the F_2 screen must be more fully examined before its widespread use.

Diagnostic-dose methods are insufficiently sensitive to allele frequencies in the most important range (10^{-6}–10^{-2}), and the F_2 screen and infield are insufficiently tested to understand (*a*) if they accurately detect resistance alleles at the sensitivity needed, (*b*) the scale of effort and cost involved in large-scale monitoring, and (*c*) if procedural changes can be implemented to improve efficiency of the screens. Caprio et al. (22) discussed other methods such as monitoring using larval-growth-inhibition assays, larval-feeding-disruption assays, and field monitoring using transgenic events with lower expression levels. The genetic basis of resistance should drive the selection of the most efficient monitoring strategy. As Caprio et al. (22) noted, when resistance is recessive, the diagnostic-dose assay will be inefficient at detecting low frequencies of resistant alleles, but if functionally dominant or at high frequencies, it may be appropriate. However, even then problems may arise if more than one locus governs resistance. Clearly, more work needs to be done on overall resistance monitoring. Perhaps the most accurate method will be to devise genomic or proteomic methods for detecting resistance genes, but even here caution must be exercised because resistance to a particular toxin may arise in multiple ways.

A remedial action plan should be in place if control failures occur. Control failures could be determined by either increases in the frequency of resistant alleles or by damage to the plant. Education of the grower and crop consultants to look for changes in the level of control is most important because they are probably going to be the first to note any suspected problems. As part of the remedial action plan, it is important to understand why resistance occurred, including better documentation of compliance efforts that growers undertook prior to the failure.

Overall Conclusion

As resistance management strategies are defined for the currently available Bt crops, it is imperative that other strategies for managing overall resistance to Bt be developed and implemented in the near future. Theoretical models suggest that pyramiding two dissimilar toxin genes in the same plant has the potential to delay the onset of resistance much more effectively than single-toxin plants released spatially or temporally and may require smaller refuges (118). The efficacy of a two-gene cotton cultivar was significantly higher than the *cry1A* one-gene cotton (61, 162). Results have shown that transgenic tobacco plants with two insecticidal genes (*cry1A* and *CpTI*) could significantly delay resistance development of *H. armigera* compared with one-gene (*cry1A*) plants (160). Other non-Bt genes will also aid in managing resistance to Bt crops.

REGULATORY AGENCIES FOR Bt PLANTS

United States

In 1986, the Office of Science and Technology Policy published its “Coordinated Framework Notice,” which declared the USDA as the lead agency for plants grown for feed, while food and feed is regulated by the Food and Drug Administration (FDA). The EPA regulates pesticides, including microbials and, in 1992 amendments to the Coordinated Framework, the EPA was given jurisdiction over pesticidal plants (96).

The National Academy of Sciences' National Research Council suggested that regulations of GE plants should be determined by "the product and not the process" (93, 98). This important concept has essentially allowed ICPs, which had been used as foliar sprays, to become registered when produced by plants. In May 1992, the FDA stated that GE plants, including Bt plants, generally fall under the GRAS (Generally Regarded As Safe) policy, which meant that foods containing transgenic genes and their products were not generally considered as food additives (51). The exception to this rule was when the introduced gene or its product is a known allergen.

This concept of "substantial equivalence" has been widely debated. Although the use of substantial equivalence has allowed companies to move their products more rapidly to market and regulatory agencies to reassure the public, some reports have been critical of the science behind this concept. As argued by Millstone et al. (88), this concept has never been properly defined, and the degree of acceptable difference between the two types of food products should be more clearly articulated. They noted that the Food and Agricultural Organization (FAO) and the World Health Organization (WHO) committee recommends that "GM foods should be treated by analogy with their non-GM antecedents, and evaluated primarily by comparing their compositional data with those from their natural antecedents, so that they could be presumed to be similarly acceptable. Only if there were glaring and important compositional differences might it be appropriate to require further tests, to be decided on a case-by-case basis." However, this argument suffers from the same vagueness because it is not clear what the phrase "glaring and important compositional differences" really means.

In January 2001, EPA issued a final rule formalizing EPA's existing process for regulating biotech crops and plants that produce their own pesticides or plant-incorporated protectants (PIPs) (148). According to the issued statement, "if the agency determines that a PIP poses little or no health or environmental risk, they will be exempted from certain regulatory requirements. As proposed in 1994, the rules will exempt from tolerance requirements the genetic material DNA involved in the production of the pesticidal substance in the plant."

China

Bt plants and other agricultural biotechnology products were primarily regulated by the Ministry of Agriculture in China from 1996 to 2001 (30). The Safety Committee for Agricultural Biological Genetic Engineering was developed to handle the safety evaluation of greenhouse experiments, environmental release, and commercial production of agricultural biotechnology products. A new Safety Administration Regulation on Agricultural Transgenic Organisms signed by the Premier of the State Council of the People's Republic of China became effective on June 7, 2001 (132). According to this regulation, labeling is required for import and sale of agricultural transgenic organisms in China. The production and business administration of seeds of Bt crops are also implemented in accordance with relevant seed regulations of province and state. An official variety name for a Bt crop is required for commercial use. Bt cotton was the first Bt crop commercialized in China in 1998, and it is the only one in the foreseeable future. Resistance management is not mandatory for the commercialization of Bt cotton in China according to the current regulatory authority, but a research program on the monitoring and management of Bt resistance was involved in the development of Bt cotton (162).

Australia

Bt cotton is the only Bt crop in the foreseeable future in Australia, although there is interest in field peas protected by an alpha-amylase inhibitor for control of pea weevils (*Bruchus pisorum*) (123). Bt cotton was reviewed by the Genetic Manipulation Advisory Committee and registered in 1996 by the National Registration Authority (14), which serves a role similar to the U.S. EPA. During 2001, the voluntary advisory system will be replaced by a Gene Technology Regulator, which will have enforcement authority. The safety of foodstuffs from transgenic crops is assessed by the Australia New Zealand Food Authority (15).

RISK ANALYSIS

As with any pesticide, it is important to understand the various and diverse effects (risks and benefits) of deployment of Bt plants on human health, pest management, the environment, and food systems and to compare these with other practices. In the United States the White House Council on Competitiveness, along with the Office of Science and Technology Policy, has articulated "a risk-based approach to regulation" (23).

Risk assessment involves four steps: hazard identification, dose-response evaluation, exposure assessment, and risk characterization. Hazard relates to a particular item causing a documented effect. Dose-response evaluation involves determining the relationship between the magnitude of exposure and probability of the adverse effect. Exposure assessment can be defined as the set of circumstances that influence the extent of exposure. Risk characterization can be viewed as a "quantitative measurement of the probability of adverse effects under defined conditions of exposure" (96). Such straightforward definitions may be useful guidelines for determining the risk of Bt plants compared with other management tactics, but the devil is in the details. Although scientists may assert that such risk assessments, despite problems of variability and extrapolation, are needed for science-based decisions, the science of risk assessment is not easily explained to the general public. Although no agricultural management practice is without risk, the public's attention to risk has been focused more on the risks of biotechnology than on the risks to the alternatives to biotechnology.

There are two distinct philosophies concerning the assessment and regulation of potentially harmful substances: (*a*) risk assessment, favored in the United States, which tries to balance risk with public health and benefits; and (*b*) the precautionary principle, used in some international treaties and increasingly in Europe, which provides more emphasis on avoiding any potential risk and less emphasis on assessing any potential benefits (43). A conference at Harvard University (77) focused on "exploring the policy and practical implications of the use of the precautionary principle in the field of biotechnology." Researchers and policymakers from several countries debated the meaning and consequences of this principle as it relates to biotechnology. Depending on one's viewpoint, the precautionary principle can be seen as unscientific and having vague and arbitrary guidelines that stifle trade and limit innovation, or it can be seen as a restraint on a fast-paced technology that may have negative consequences across many social and biological fronts. Thus, some proponents of the precautionary principle demand that governments ban the planting of Bt plants until questions about their safety are more fully answered. Already the precautionary principle regulates policy decisions in Germany and Switzerland and "may soon guide the policy of all of Europe" (12). The principle has been mentioned in the United Nations Biosafety Protocol regulating trade in GE products.

How much do we need to know to implement a new strategy? In the 1970s and 1980s, entomology embraced a systems-science approach in determining optimal management of agroecosystems. Systems science was seen as an aid in dealing with complexity by providing techniques to integrate information on diverse systems, but the larger problem is the sheer number of possible interactions in agroecosystems and the time, effort, and expense required to gather and comprehend the information on them all. Hence, as usual, scientists are left with the question of how much do we need to know in order to implement? As with any technology, Bt plants were deployed without full knowledge of their effects but with a conviction that the risks would be fewer than current technology and that the benefits of GE crops would be greater.

The essential debate about the use of biotechnology, including the use of Bt plants, should focus on comparing the technology with existing or developing technologies in at least the following areas: food safety and human health, environmental compatibility (including the effects on nontarget organisms, water supplies), benefits and risks to the producer and consumer, effects on food systems, and issues of social justice (a complex series of often important but hard-to-quantify issues). Additionally, one should examine each on a crop-by-crop basis.

FOOD SAFETY

An article in *Consumer Reports* (36) heightened the awareness in the United States of how food products from GE plants move into supermarkets. Although the article stated "there's no evidence such (genetically engineered) foods aren't safe to eat," the implication was that there was no evidence stating they were safe to eat. The principal food safety concerns for Bt plants are potential toxicity and allergenicity of the newly introduced proteins, changes in nutrient composition of the plants, and the safety of antibiotic resistance-marker-encoded proteins included in the transgenes. A review of these issues is presented in a joint FAO/WHO publication (154). As noted by EPA (146), "several types of data are required for the Bt plant-pesticides to provide a reasonable certainty that no harm will result from the aggregate exposure of these proteins. The information is intended to show that the Bt protein behaves as would be expected of a dietary protein, is not structurally related to any known food allergen or protein toxin, and does not display any oral toxicity when administered at high doses." EPA does not conduct long-term studies because it believes that the instability of the protein in digestive fluids eliminates this need, in line with their policy of substantial equivalence. The in vitro–digestion assays used simply attempt to confirm that the Bt protein is degraded into small peptides or amino acids in solutions that mimic digestive fluids, but the assays are not intended to provide information on the toxicity of the protein itself. Acute oral toxicity is assessed through feeding studies with mice using a pure preparation of the plant-pesticide protein at doses of >5000 mg/kg bodyweight. None of the Bt proteins registered as plant pesticides in the United States has shown any significant effect (18, 146, 154). The potential allergenicity of a Bt protein can be examined through the in vitro–digestion assays, but further assessment is done by examining amino acid homology against a database of known allergens (154).

Comparisons for allergenicity have also been made between foliar Bt products and Bt proteins expressed in plants. A commercial Bt product, Javelin, has been separated into water-soluble components, Bt spores, and Bt endotoxin protein, and farmworkers were subjected to skin prick tests (17), which are routinely used to test for allergic reactions to foods or other substances. Only the Javelin extracts representing the water-soluble portions and the spores gave positive reactions. Based on these tests, Felsot (48) concluded "results of this investigation should partially allay recent concerns about the occurrence of possible adverse health effects in consumers after exposure to transgenic foods." Furthermore, "it is unlikely that consumers would develop allergic sensitivity after oral exposure to transgenic foods (e.g., tomatoes, potatoes) that currently contain the gene encoding this [the Bt] protein."

Because of the StarLink situation (registration of this Cry9C product only for animal feed, although it became commingled with products for human consumption), the EPA (143, 149) addressed more fully the allergenicity concerns with Cry9C during its Scientific Advisory Panel report issued on December 5, 2000. This report expressed "the consensus of the Panel that while Cry9C has a 'medium likelihood' to be an allergen, the combination of the expression level of the protein and the amount of corn found to be commingled poses a 'low probability' of sensitizing individuals to Cry9C." Heat studies are also conducted because many of these Bt plant products are processed into foods. A key issue is that not all foodstuffs prepared from GE crops are GE. Both protein and DNA are destroyed during the processing of highly refined foodstuffs such as oils and sugars. This is especially true for cottonseed oil, which must be heavily refined to remove toxic secondary plant compounds. Not only is there no DNA or protein in cottonseed oil, there is no consistent difference between GE and non-GE cottonseed oil in compositional analyses (15). Cry1Ab and Cry1Ac became inactive in processed corn and cottonseed meal (146), but Cry9C was stable when exposed to simulated gastric digestion and to temperatures at 90°C (143) and was therefore not permitted for human consumption, although it was allowed for animal consumption, a decision that led to the StarLink situation. Chassy (29) notes that the concentration of Cry proteins in transgenic plants is usually well below 0.1% of the plant's total protein, and none of the Cry proteins have been demonstrated to be toxic to humans nor have they been implicated to be allergens. Furthermore, they do not contain sequences resembling relevant allergen epitopes. However, he also notes that it is impossible to provide consumers assurance of absolute-zero risk, largely owing to the inadequacy of methods to screen for novel and previously unreported toxicity or allergenicity; (but that) the zero-risk standard that is applied to this new technology far exceeds the standard used for novel crops produced by conventional methods.

In contrast to concerns about toxicity and allergens from GE, there is clear evidence for health benefits from Bt corn. Fusarium ear rot is a common ear rot disease in the Corn Belt and the primary importance of this disease is its association with mycotoxins, particularly the fumonisins, a group of mycotoxins that can be fatal to horses and pigs and are probable human carcinogens (91). Field studies have demonstrated that hybrids containing the MON810 and Bt11 Bt events experience significantly lower incidence and severity of Fusarium ear rot and yield corn with lower fumonisin concentrations than their non-Bt counterparts (5, 92).

Because the majority of corn worldwide is fed to livestock, questions arise about its suitability as animal feeds. In a study using Bt corn silage on the performance of dairy cows, the authors found no significant differences between Bt and non-Bt corn hybrids in lactational performance or ruminal fermentation (49). A summary of studies on Bt crops fed to chicken-broilers, chicken-layers, catfish, swine, sheep, lactating dairy cattle, and beef cattle was compiled by the Federation of Animal Societies (47). In a review using these studies, Faust (46) concludes that there are "no detrimental effects for growth, performance, observed health, composition of meal, milk, and eggs, etc."

In a review of the safety issues associated with DNA in animal feed derived from GE crops, Beever & Kemp (16) examined the range of issues from protein safety to the uptake and integration of foreign DNA to the potential for antibiotic resistance-marker DNA and concluded "consumption of milk, meat and eggs produced from animals fed GM crops should be considered as safe as traditional practices." Reports issued by the Institute of Food Technologists (70) have similar conclusions and state that "biotechnology processes tend to reduce risks because they are more precise and predictable than conventional techniques."

THE SOCIAL ISSUES

Consolidation of Agriculture

Agriculture has changed dramatically both in how and where food is produced. Since the mid-1950s, agriculture has become bigger and more specialized and is now one of the world's largest industries, employing 1.3 billion people and producing $1.3 trillion worth of goods each year (40). No longer is the world's $20 billion commercial seed market as diversified as it once was. Life science companies with capabilities in biotechnology that were involved in agriculture have bought seed companies in order to increase the value of the seed itself by making pest–protected crops like Bt plants. Ironically, as pressure is being applied to restrict the use of pesticidal plants, many of the companies producing the seeds also produce pesticides and are "making more money by selling herbicides and insecticides now" (103).

The percentage of people working in agriculture has also declined. Even in France and Germany, the number of farmers has dwindled by 50% since 1978, and in the Organization for Economic Cooperation and Development as a whole, the number of farms has declined by 1.5% per year, and farmers now make up only 8% of the labor force (40). Hand in hand with the consolidation of the production sector is the consolidation of the retail market sector, and the consolidation of the market sector also allows it to hold influence over its suppliers. In the United States, consolidation of the market sector lags behind Europe; in Germany, for example, five supermarkets control nearly two thirds of the market (40). Depending on one's viewpoint, changes in agricultural production have what can be considered benefits (e.g., lower food prices) or liabilities (e.g., consolidation of the food system). It is important to recognize that the process of market consolidation began long before GE crops. Certainly, some of the concern about agricultural biotechnology can be traced back to concern about multinationals (41) and who controls the technology, who has access to the technology, and whether there is freedom of choice to use or avoid the technology.

Corporate relationships with universities (99, 113) and control of a public resource such as a bacterium that produces insecticidal properties may make some uncomfortable, but this may be the only practical means to make sure the technology is deployed and pest management and environmental and health benefits accrue. We agree with Marvier (85): "Despite recent studies that highlight possible risks, plants engineered to express Bt toxin are almost certainly safer than most chemical pesticides, which generate well-established dangers for nontarget arthropods." The use of foliar sprays of Bt has been limited because of its lack of persistence, coverage, cost, and proper dose (117). It is only when the genes of Bt have been incorporated into plants that this once-minor insecticide has become a major tool in pest management. The Entomology Society of America has concluded that GE crops "could facilitate a shift away from reliance on broad-spectrum insecticides toward more biointensive pest management" and "may reduce insecticide use" but that such "evaluations should be done on a case-by-case analysis of the risks and benefits" (42).

Trade Issues and the Global Food Supply

While farmers in the United States were rapidly adopting Bt crops, opponents were mobilizing and putting pressure on processors and retailers to avoid their use (43), and this led to some unusual situations. Novartis, a producer of Bt corn that also owns Gerber Baby Foods and some other health foods, announced that it would eliminate GE ingredients from all its food products, although admitting that this was not based on any doubt about the safety of the food but rather on consumers being "wary of them" (43). On the other hand, at least for the time being, some large companies continue to accept biotech crops, and some companies such Lumen Foods, the largest soybean processor in the United States, have taken a proactive stance for biotechnology (7).

On an international level, resistance shown by consumers in Europe and other countries to foods containing GE products created problems for both the private and public sectors. In the international debate, there are three main sets of questions about GE crops. The first involves identifying the economic, social, and ethical benefits and costs associated with specific GE products; the second involves adequate regulations; and the third set involves the legal and effective ownership of the genetic material (102). Such complex questions have been put on the table, but discussion of them will be influenced by diverse cultures (European, American, or other developed or developing countries) (128) and will likely influence trade policies for biotechnology in the future (76).

Trade issues in the form of domestic and international scales were seen with StarLink, the variety of GE corn not approved for human consumption. Although StarLink only represented 1% of the total corn harvested in the United States in 2000, it was detected in food products such as taco shells. Registration of StarLink was voluntarily pulled from the market and a number of lawsuits are pending. In January 2001, Aventis agreed to pay millions in compensation to farmers across the United States, and the estimated cost ranged from $100 million to $1 billion (13). The USDA also announced on March 8, 2001, that it will buy back between 300,000 and 400,000 bags of corn seeds that contain traces of Cry9C. This may cost the government between $15 and 20 million, but it was done to ensure a stable and predictable market. On March 9, 2001, the EPA announced it would no longer provide split registrations for animal and human feed. On a more localized level, organic farmers are concerned their crops may become contaminated by neighbors producing GE crops. Issues of liability in such situations are not clear but are important for both parties because each can claim that his right to farm is being questioned. Difficult legal and ethical issues are raised by this technology.

Labeling

Considerable discussion on labeling occurs worldwide. Such discussions include not only whether GE foods are safe to eat but also their environmental and economic impacts compared with other production methods, whether GE foods can be segregated in a complex food system, and who will pay the costs for ensuring the integrity of labeling. An important question is whether labeling will help consumers make an informed choice. In the EU, foods must be labeled as containing GE products if they contain >1% GE products, and such labeled products may provoke a strong negative reaction in the market. Consequently Europe is moving to "traceability" or "process labeling" by which producers must declare they did not use GE in their production, and this will likely discourage the use of GE crops. This approach has tremendous challenges in monitoring and enforcing such a policy, as well as implications within the World Trade Organization. Furthermore, it is unclear what the costs of such a system will be and who will bear the costs.

On January 17, 2001, FDA issued a proposed rule and a guideline that supplement existing regulations of foods derived from biotechnology crops (101). The proposed rule would require food developers of new biotech products to notify the agency at least 120 days in advance of their intent to market a food or animal feed developed through biotechnology and to provide appropriate information to demonstrate that the product is as safe as the conventional counterpart. FDA also announced that this information would be made public to increase the transparency of the agency's review process for such products. These proposed rules were supported by the food industry, which viewed them as a means to increase consumer confidence in biotechnology. As of this writing, the debate about whether GE products will be labeled in the United States is unresolved. Whether labeling items as containing GE products will improve public confidence in biotechnology or lead to a decline in its use remains to be seen. Some products are now being labeled as free of genetic engineering, although they have proved otherwise (21). It will be difficult, if not impossible, to have assurance that a food item containing multiple ingredients (e.g., pizza) does not contain a biotechnology product or that an animal product did not result from an animal fed some GE feed or medicine (29). Tracking the origins of all ingredients used in a food supply or reliably detecting GE products in a food will present unprecedented challenges.

Ethics

An area of study that is often not explicitly stated but influences the acceptability of biotechnology may be called ethics. The term ethics is often meant to be a set of principles of conduct governing an individual or a set of moral principles or values. The Nuffield Council (106) examined some of the ethical issues raised by the development and application of agricultural biotechnology in world agriculture and food security. It guided its discussion on agricultural biotechnology by considering three main ethical principles: the principle of general human welfare, the maintenance of people's rights, and the principle of justice. The delegates found broad differences in the ways these issues needed to be dissected—from the purely technical aspects to the more complex issues such as whether moving genes between organisms was unnatural. The conference occurred at the time of demands for the banning of GE foods and moratoria on plantings, but the delegates did not believe that there is enough evidence of actual or potential harm to justify a moratorium on either GE crop research, field trials, or limited release into the environment at this stage. Most importantly, the panel members urged the development of "a powerful public policy framework to guide and regulate the way GM technology is applied in the UK" to ensure that public concerns are addressed, and they urged that "that an over-arching, independent biotechnology advisory committee is established to consider within a broad remit, the scientific and ethical issues together with the public values associated with GM crops." In the United States, the debate on the ethics of agricultural biotechnology has been led by Thompson (138) and Comstock (35), the latter whose earlier writings were decidedly against biotechnology but who is now a cautious proponent of GE technology.

THE FUTURE

No technology, new or old, is without risks and controversy. For biotechnology, touted as the third-greatest revolution in technology (3), it is appropriate that not only the technical but also the social issues surrounding the dialogue be discussed. Scientists need to be heard in this present dialogue. The reporting of biotech issues has changed markedly since 1997 and "moved from being a scientific issue to being a social issue" (1). Biotechnology is now a major topic in the public media. In late 1999, the *New York Times* was running "almost one article per day on this (biotech) topic" (1). On the other hand, university scientists are being used less and less as sources for stories, and by September 2000 only 12% of the news stories quoted university scientists, whereas environmental activist groups such as Greenpeace, the Environmental Defense Fund, and the Union of Concerned Scientists were used increasingly as sources of news (2). Additionally, Abbott (2) notes that even major newspapers such as the *New York Times* and the *The Times* (London) are more than twice as likely to use a quote from one of these sources than from university scientists. Scientists have the obligation to conduct their work carefully and present their findings in a nonsensational fashion (126). In addition to the responsibility of the scientific community, there is also a responsibility for society to help educate itself on biotechnology. This is an increasingly difficult challenge because of the public's level of scientific illiteracy, which has led to a growing distrust of science and technology (55).

Stewart & Wheaton (133) state that "there is no evidence that current products of GM crops produced in the US are harmful to the environment or human health" but suggest that we need more solidly designed ecological experiments to not only satisfy regulatory requirements but to also show "what parameters need to be followed in post-commercialization monitoring." The authors state that "if combined agronomic and ecological studies had occurred more frequently in the past, current public perception of GM might be quite different, and the paranoia arising from a sense of being uninformed might be diminished." These thoughts should be kept in mind as we discover the possibilities and liabilities of insect control through plants expressing Bt proteins.

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LITERATURE CITED

1. Abbott E. 2000. Media coverage of GMOs in the USA and UK: Who's quoted and what's said. Presented at Cornell Conf. *Informing the Dialogue about Agricultural Biotechnology*, Nov. 15–16. Ithaca, NY. http://www.nysaes.cornell.edu/comm/gmo/
2. Abbott E. 2001. Scientists being ignored in media coverage of GMOs. *Greenlee Sch. Journal. Commun. Newsl.* 60:No. 68. 3 pp.
3. Abelson PH. 1998. A third technological revolution. *Science* 279:2019
4. Ahmad M. 1999. *Initial frequencies of alleles for resistance to* Bacillus thuringiensis *toxins in field populations*. PhD thesis. Univ. Adelaide. 215 pp.
5. Am. Phytopathol. Soc. 2001. *Genetically modified insect resistant corn: implications for disease management*. http://www.scisoc.org/feature/BtCorn/Top.html
6. Ammann K. 1999. Debate 991120b. *Nontarget organisms, literature survey Novartis*. klaus.ammann@ips.unibe.ch
7. Ammann K. 2000. Debate 2000'0224b: *Good news from the food front*. klaus.ammann@ips.unibe.ch
8. Andow D, Alstad DN. 1999. Credibility interval for rare resistance allele frequencies. *J. Econ. Entomol.* 92:755–58
9. Andow DA, Alstad DN, Pang YH, Bolin PC, Hutchison WD. 1998. Using an F_2 screen to search for resistance alleles to *Bacillus thuringiensis* toxin in European corn borer (Lepidopter: *Crambidae*). *J. Econ. Entomol.* 91:579–84
10. Andow DA, Hutchison WD. 1998. *Bt-*corn resistance management. In *Now or Never: Serious New Plans to Save a Natural Pest Control*, ed. M Mellon, J Rissler, pp. 19–66. Washington, DC: Union Concerned Sci.
11. Andow DA, Olson DM, Helmich RL, Alstad DN, Hutchison WD. 1999. Frequency of resistance to *Bacillus thuringiensis* toxin Cry1Ab in an Iowa population of European corn borer (Lepidopter: *Crambidae*). *J. Econ. Entomol.* 92:26–30
12. Appell D. 2001. The new uncertainty principle. *Sci. Am.* Jan.:18–19
13. Associated Press. 2001. Farmers to receive millions under tainted corn agreement. *Rochester Democr. Chron.*, Jan. 24, p. 4A
14. Aust. NZ Food Authority (ANZFA). 2001. *Applications and Proposals with*

ANZFA for Genetically Modified Foods. http://www.anzfa.gov.au/

15. Aust. NZ Food Authority (ANZFA). 2001. *Food standards code*. http://www.anzfa.gov.au/foodstandards/foodstandardscodecontents/index.cfm
16. Beever DE, Kemp CF. 2000. Safety issues associated with the DNA in animal feed derived from genetically modified crops. A review of the scientific and regulatory procedures. *Nutr. Abstr. Rev.* 70(3):175–82
17. Bernstein IL, Bernstein JA, Miller TS, Bernstein DL, Lummus L, et al. 1999. Immune responses in farm workers after exposure to *Bacillus thuringiensis* pesticides. *Environ. Health Perspect.* 107(7):575–82
18. Betz FS, Hammond BG, Fuchs RL. 2000. Safety and advantages of *Bacillus thuringiensis* protected plants to control insect pests. *Reg. Toxicol. Pharmacol.* 32:156–73
19. Bourguet D, Bethenod MT, Pasteur N, Viard F. 2000. Gene flow in the European corn borer *Ostrinia nubialis*: implications for the sustainability of transgenic insecticidal maize. *Proc. R. Soc. London Ser. B* 267:117–22
20. Bushman L, Sloderbeck P, Guo Y, Martin V. 1998. Corn borer resistance and grain yield of Bt and non-Bt corn hybrids at St. John, KS, 1997. 7 pp. http://www.oznet.ksu.edu/SWAreaOffice/Entomology/98FieldDay/FDBt97SJ.pdf
21. Callahan P, Kilman S. 2001. Seeds of doubt: Some ingredients are genetically modified, despite labels' claims—lab tests finds altered DNA in Soy O's, Veggie Bacon, belying marketing pitch—no proven dangers to health. *Wall St. J.* April 5. p. 5
22. Caprio MA, Summerford DV, Simms SR. 2000. Evaluating plants for suitability in pest and resistance management programs. See Ref. 81a, pp. 805–28
23. Carpenter JE. 2001. Case studies in benefits and risks of agricultural biotechnology: Roundup ready soybeans and Bt field corn. *Natl. Cent. Food Agric. Policy.* http://www.ncfap.org/pup/biotech/benefitsandrisks.pdf
24. Carpenter JE. 2001. GM crops and patterns of pesticide use. *Science* 292:637–38
25. Carpenter JE, Gianessi LP. 2001. Agricultural biotechnology: updated benefit estimates. *Natl. Cent. Food Agric. Policy.* http://ncfap.org/pup/biotech/updatedbenefits.pdf
26. Carozzi N, Koziel M, eds. 1997. *Advances in Insect Control: The Role of Transgenic Plants*. London: Taylor & Francis. 301 pp.
27. Carriere Y, Dennehy TJ, Pedersen B, Haller S, Ellers-Kirk C, et. al. 2001. Large-scale management of insect resistance to transgenic cotton in Arizona: Can transgenic insecticidal crops be sustained? *J. Econ. Entomol.* 94:315–25
28. Casagrade RA. 1987. The Colorado potato beetle: 125 years of mismanagement. *Bull. Entomol. Soc. Am.* 33(3):142–50
29. Chassy B. 2000. Insuring the safety of foods derived from agricultural biotechnology: present reality and future prospects. (See Ref. 1) Presented at Cornell Conf. *Informing the Dialogue about Agricultural Biotechnology*, Nov. 15–16, Ithaca, NY. http://www.nysaes.cornell.edu/comm/gmo/
30. Chinese Ministry Agric. 1996. *Safety administration implementation regulations on agricultural biological genetic engineering*, pp. 52–67. Beijing, China: Minist. Agric.
31. CIMMYT. 1999. *1997–98 CIMMYT World Maize Facts and Trends; Maize Production in Drought-Stressed Environments: Technical Options and Research Resource Allocation*. Mexico, DF: CIMMYT
32. Clark D, Long T, Pyke B. 1998. The performance of INGARD® cotton in Australia in the 1997/98 season. Narrabri, Aust.: Cotton R&D Corp. Occas. Pap. 40 pp.

33. Clark D, Long T, Pyke B. 1999. The performance of INGARD® cotton in Australia in the 1998/99 season. Narrabri, Aust.: Cotton R&D Corp. Occas. Pap. 46 pp.
34. Cohen MB, Gould F, Bentur JS. 2000. *Bt* rice: practical steps to sustainable use. *Int. Rice Res. Notes* 25(2):5–10
35. Comstock G. 2000. *Vexing Nature? On the Ethical Case Against Biotechnology*. Boston: Kluwer. 312 pp.
36. Consumer Rep. 1999. Seeds of change. *Consumer Rep.* Sept.:41–45
37. Crawley MJ, Brown SL, Hails RS, Kohn DD, Rees M. 2001. Biotechnology: transgenic crops in natural habitats. *Nature* 409:682–83
38. Doebley J. 1990. Molecular evidence for gene flow among *Zea* species. *BioScience* 40:443–48
39. Douches DS, Westedt AL, Zarka K Schroeter B, Grafius EJ. 1998. Transformation of potato with the Bt-cry5 transgene to combine natural and engineered resistance mechanisms to control tuber moth. *HortScience* 33:1053–56
40. Economist, The. 2000. *Agriculture and technology*. Spec. rep. *The Economist* March 25. 16 pp.
41. Economist, The. 2000. The world's view of multinationals. *The Economist* Jan. 29, pp. 21–22
42. Entomol. Soc. Am. 2001. *Position statements on transgenic insect-resistant crops*. http://www.entsoc.org/about_esa/statements/transgenic.html
43. Environ. Media Serv. 2000. *Reporters' guide: genetic engineering in agriculture*. http://www.ems.org/food/media_guide.html
44. Escher N, Käch B, Nentwig W. 2000. Decomposition of transgenic *Bacillus thuringiensis* maize by microorganisms and woodlice *Porcellio scaber* (Crustacea: Isopoda). *Basic Appl. Ecol.* 1:161–69
45. Falck-Zepeda J, Traxler G, Nelson RG. 2000. Surplus distribution from the introduction of a biotechnology innovation. *Am. J. Agric. Econ.* 82:360–69
46. Faust MA. 2000. Straight talk about biotech crops for the livestock, dairy and meat industries. *Proc. Excel Food Saf. Technol. IV*. Wichita, KS. 10 pp.
47. Fed. Anim. Sci. Soc. 2001. *Communications. References-feeding transgenic crops to livestock.* http://www.fass.org/REFERENC.htm
48. Felsot AS. 2000. Insecticidal genes. Part 2: Human health hoopla. *Agric. Environ. News*. Issue 168. 5 pp. http://www.tricity.wsu.edu/aenews/April00AENews/Apr00AENews.htm#anchor5338542.
49. Folmer JD, Grant RJ, Milton CT, Beck JF. 2000. Effect of Bt corn silage on short-term lactational performance and ruminal fermentation in dairy cows. *J. Dairy Sci.* 83:1182 (Abstr. 272)
50. Food Agric. Organ. UN (FAO). 2000. *Agriculture data*. http://apps.fao.org/page/collections?subset=agriculture
51. Food Drug Admin. 1992. FDA Statement of Policy: foods derived from new plant varieties. *Fed. Regist.* 57:22984
52. Forrester N. 1997. The benefits of insect resistant cotton. In *Commercialisation of Transgenic Crops: Risk, Benefit and Trade Considerations*, ed. GD McLean, P Waterhouse, G Evans, MJ Gibbs, pp. 239–42. Canberra: Coop. Res. Cent. Plant Sci. Bur. Stat.
53. Frisvold GB, Tronstad R, Mortensen J. 2000. Adoption of Bt cotton; regional differences in producer costs and returns. *Proc. Beltwide Cotton Conf.* 2:337–40. Memphis, TN: Natl. Cotton Counc. Am.
54. Frutos R, Rang C, Royer M. 1999. Managing resistance to plants producing *Bacillus thuringiensis* toxins. *Crit. Rev. Biotechnol.* 19:227–76
55. Fumento M. 1999. Unpopular science: Public distrust of science and technology can be deadly. *Am. Outlook* Summer 23–25. http://www.fumento.com/
56. Gebhard F, Smalla K. 1999. Monitoring field releases of genetically modified sugar beets for persistance of transgenic plant DNA and horizontal gene

transfer. *FEMS Microbiol.* 28(3):261–72
57. Gianessi LP, Carpenter JE. 1999. *Agricultural Biotechnology: Insect Control Benefits*. Washington, DC: Natl. Cent. Food Agric. Policy. 98 pp.
58. Gould F. 1998. Sustainability of transgenic insecticidal cultivars: integrating pest genetics and ecology. *Annu. Rev. Entomol.* 43:701–26
59. Gould F, Anderson A, Jones A, Sumerford D, Heckel DG, et al. 1997. Initial frequency of alleles for resistance to *Bacillus thuringiensis* toxins in field populations of *Heliothis virescens*. *Proc. Natl. Acad. Sci. USA* 94:3519–23
60. Gray ME. 1999. Transgenic insecticidal cultivars for corn rootworms: resistance management considerations. *Proc. Crop Prot. Technol. Conf.*, pp. 50–58. Urbana-Champaign: Univ. Ill.
61. Greenplate JT, Pen SR, Shappley Z, Oppenhuizen M, Mann J, et al. 2000. Bollgard II efficacy: quantification of total lepidopteran activity in a 2-gene product. *Proc. Beltwide Cotton Conf.* 2:1041–43. Memphis, TN: Natl. Cotton Counc. Am.
62. Guo SD. 1995. Engineering of insect-resistant plant with *Bacillus thuringiensis* crystal protein genes. *Sci. Agric. Sin.* 28(5):8–13
63. Guo SD, Cui H, Xia L, Wu D, Ni WC, et al. 1999. Development of bivalent insect-resistant transgenic cotton plants. *Sci. Agric. Sin.* 28(5):1–7
64. Hansen LC, Obrycki JJ. 2000. Field deposition of Bt transgenic corn pollen: lethal effects on the monarch butterfly. *Oecologia* 125:241–48
65a. Hellmich RL, Rice ME, Pleasants JM, Lam WK. 2000. Of monarchs and men: possible influences of Bt corn in the agricultural community. *Proc. Integr. Crop Management Conf.*, pp. 85–94. Ames: Iowa State Univ. Ext.
65b. Hellmich RL, Siegfried BD. 2001. *Bt* corn and the monarch butterfly: research update. In *Genetically Modified Organisms in Agriculture*, ed. GC Nelson, pp. 283–89. New York: Academic
66. Hilbeck A, Baumgartner M, Freid PM, Bigler F. 1998. Effects of *Bacillus thuringiensis* corn-fed prey on mortality and development time of immature *Chrysoperla carnae*. *Environ. Entomol.* 27:480–87
67. Hilbeck A, Moar WJ, Pusztai-Carey M, Filippini AM, Bigler F. 1998. Toxicity of *Bacillus thuringiensis* Cry1Ab toxin to the predator *Chrysoperla carnae*. *Environ. Entomol.* 27:1255–63
68. Hilbeck A, Moar WJ, Pusztai-Carey M, Filippini AM, Bigler F. 1999. Prey-mediated effects of Cry1Ab toxin and protoxin and Cry2A protoxin on the predator *Chrysoperla carnae*. *Entomol. Exp. Appl.* 91:305–16
69. Hodgson J. 1999. Monarch *Bt* corn paper questioned. *Nat. Biotechnol.* 17:627
70. Inst. Food Technol. 2000. *Expert Report on Biotechnology and Foods: Human Food Safety Evaluations of rDNA Biotechnology-derived Foods*. http://www.ift.org/resource/index.shtml
71. Int. Life Sci. Inst., Health Environ. Sci. Inst. (ILSI HESI). 1999. *An evaluation of insect resistance management in Bt field corn: a science-based framework for risk assessment and risk management.* Report of an expert panel, Nov. 23. Washington, DC: ILSI
72. James C. 1999. Global status of commercialized transgenic crops: 1999. *ISAAA Briefs* No. 17. Ithaca, NY: ISAAA. 65 pp.
73. James C. 2000. Global status of commercialized transgenic crops: 2000. *ISAAA Briefs* No. 21. Ithaca, NY: ISAAA
74. Jansens SJ, Cornelissen M, DeClercq R, Reynaerts A, Peferoen M. 1995. *Phthorimaea operculella* resistance in potato by expression of *Bacillus thuringiensis* CryIA(b) insecticidal crystal protein. *J. Econ. Entomol.* 88:1469–76
75. Jia SR, Guo SD, An DC, eds. 2001. *Transgenic Cotton*. Beijing: Science. 281 pp.

76. Jones ME. 1999. *Politically corrected science: the early negotiations of U. S. agricultural biotechnology policy*. PhD thesis. Va. Polytech. Inst., Blacksburg, Va. 393 pp.
77. Kennedy Sch. Gov. 2000. *International Conference on Biotechnology in the Global Economy: Science and the Precautionary Principle*, Sept. 22–23 http://www.cid.harvard.edu/cidbikotech/biocon fpp/
78. Knight A. 2000. *Science and the Press.* http://agbioview.listbot.com
79. Koziel MG, Beland GL, Bowman C, Carozzi N, Crenshaw R, et al. 1993. Field performance of elite transgenic maize plants expressing an insecticidal protein gene derived from *Bacillus thuringiensis*. *Bio/Technology* 11:195–200
80. Krattiger AF. 1997. Insect resistance in crops: a case study of *Bacillus thuringiensis* (Bt) and its transfer to developing countries. *ISAAA Briefs* No. 2, p. 42. Ithaca, NY: ISAAA
81. Kwint P, Pyke B. 2000. *The performance of INGARD® cotton in Australia in the 1999/2000 season.* Narrabri, Aust.: Cotton R&D Corp. Occas. Pap. 46 pp.
81a. Lacey LL, Kaya HK, eds. 2000. *Field Manual of Techniques in Invertebrate Pathology*. Dordrecht: Kluwer
82. Long A, Pyke B, Slack-Smith P. 1997. *The performance of INGARD® cotton in Australia in the 1996/97 season.* Narrabri, Aust.: Cotton R&D Corp. Occas. Pap. 42 pp.
83. Losey J, Raynor L, Carter ME. 1999. Transgenic pollen harms monarch larvae. *Nature* 399:214
84. Luttrell RG, Fitt GP, Ramalho FS, Sugonyaev ES. 1994. Cotton pest management. *Annu. Rev. Entomol.* 39:517–91
85. Marvier M. 2001. Ecology of transgenic crops. *Am. Sci.* 89:160–67
86. Mason CE, Rice ME, Calvin DD, Van Duyn JW, Shower WB, et al. 1996. *Eur. Corn Borer: Ecology and Manag. North Cent. Reg. Ext. Publ. No. 327*. Ames: Iowa State Univ. 57 pp.
87. Metcalf RL, Metcalf RA. 1993. *Destructive and Useful Insects: Their Habits and Control*. New York: McGraw-Hill. 5th ed.
88. Millstone E, Brunner E, Mayer S. 1999. Beyond 'substantial equivalence'. *Nature* 401:525–26
89. Mohammed A, Douches DS, Tett W, Grafius E, Coombs J, et al. 2000. Evaluation of potato tuber moth resistance in tubers of Bt-cry5 transgenic potato lines. *J. Econ. Entomol.* 93:472–76
90. Morales AA. 2000. *The Mexican experience with insect resistant Bt transgenic crops*. Presented at Soc. Invert. Pathol., Aug. 13–18, Guanajuato, Mex. (Abstr.)
91. Munkvold GP, Desjardins AE. 1997. Fumonisins in maize: Can we reduce their occurrence? *Plant Dis.* 81:556–65
92. Munkvold GP, Hellmich RL, Rice LG. 1999. Comparison of fumonisin concentrations in kernels of transgenic Bt maize hybrids and non-transgenic hybrids. *Plant Dis.* 83:130–38
93. Natl. Acad. Sci. 1987. *Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues*. Washington, DC: Natl. Acad. Press. 187 pp.
94. Natl. Acad. Sci. 2000. *The Future Role of Pesticides in US Agriculture*, ed. R Pool, J Esnayra. Washington, DC: Board Agric. Nat. Resourc. 301 pp. http://books.nap.edu/books/0309065267/html/
95. Natl. Acad. Sci. 2000. *Ecological Monitoring of Genetically Modified Crops: A Workshop Summary*, ed. R Pool, J Esnayra. Washington, DC: Board Agric. Nat. Resourc. 60 pp. http://books.nap.edu/nap-cgi/newsrch.cgi?term=ecological+monitoring
96. Natl. Acad. Sci. 2000. *Genetically Modified Pest-protected Plants: Science and Regulation*. Washington, DC: Natl. Acad. Press. 292 pp.
97. Natl. Acad. Sci. 2000. *Environmental Impacts Associated with Commercialization of Transgenic Plants: Issues and*

Approaches to Monitoring. http://www4.nas.edu/cp.nsf/57b01c7b1b6493c485256555005853cf/f744e78d2c4a6365852568fc004788502? OpenDocument

98. Natl. Res. Counc. (NRC). 1989. *Field Testing Genetically Modified Organisms: Framework for Decision.* Washington, DC: Natl. Acad Press
99. *Nature*. 2001. Is the university-industrial complex out of control? *Nature* 409:119
100. *Nat. Biotechnol*. 1999. Agricultural biotechnology. *Nat. Biotechnol.* 17:612–14
101. *Nat. Biotechnol*. 2000. GM food policy upheld. *Nat. Biotechnol.* 18:1128
102. Nelson GC, Josling T, Bullock D, Unnevehr L, Rosegrant M, et al. 1999. The economics and politics of genetically modified organisms in agriculture: implications for WTO 2000. *Univ. Ill. at Urbana-Champaign Bull. 809*. 119 pp.
103. *New Sci.* 2000. Opinion interview. *New Sci.* 169:66–69
104. Nielson KM, Bones AM, Smalla K, Van Elsas JD. 1998. Horizontal gene transfer from transgenic plants to terrestial bacteria—a rare event? *FEMS Microbiol. Rev.* 22(2):79–103
105. Nigh R, Benbrook C, Brush S, Garcia-Barrios L, Ortega-Paczka R, Perales HR. 2000. Transgenic crops: a cautionary tale. *Science* 287:1927
106. Nuffield Counc. Bioethics. 1999. *Genetically Modified Crops: The Ethical and Social Issues*. London: Nuffield Counc. Bioethics. 164 pp. http://www.nuffield.org.uk/bioethics/publication/modified crops/rep0000000075.html
107. Onstad D, Gould F. 1998. Modeling the dynamics of adaptation to transgenic maize by European corn borer. *J. Econ. Entomol.* 91:585–93
108. Ostlie KR, Hutchinson WD, Hellmich RL. 1997. Bt corn and European corn borer: long-term success through resistance management. *North Cent. Reg. Ext. Publ. 602*. St. Paul: Univ. Minn. Ext. Serv.
109. Paget E, Lebrun M, Freyssinet G, Simonet P. 1998. The fate of recombinant plant DNA in soil. *Eur. J. Soil Biol.* 34(2):81–88
110. Peck SL, Gould F, Ellner SP. 1999. Spread of resistance in spatially extended regions of transgenic cotton: implications for management of *Heliothis virescens*. *J. Econ. Entomol.* 92:1–16
111. Perlak FJ, Deaton RW, Armstrong TA, Fuchs RL, Sims SR, et al. 1990. Insect resistant cotton plants. *Bio/Technology* 8:939–43
112. Perlak FJ, Fuchs RL, Dean DA, McPherson SL Fischhoff DA. 1991. Modification of coding sequence enhances plant expression of insect control protein genes. *Proc. Natl. Acad. Sci. USA* 88:3325–28
113. Press E, Washburn J. 2000. The kept university. *Atlan. Mon.* http://www.theatlantic.com/issues/2000/03/press. htm
114. Pray CE, Ma D, Huang J, Qiao F. 2001. Impact of Bt cotton in China. *World Dev.* 29:813–25
115. Raynor GS, Ogden EC, Hayes JV. 1972. Dispersion and deposition of corn pollen from experimental sources. *Agron. J.* 64:420–27
116. Rice WC, Choo HY. 2000. Rice pests. See Ref. 81a, pp. 425–65
117. Roush RT. 1994. Managing pests and their resistance to *Bacillus thuringiensis*: Can transgenic crops be better than sprays? *Biocontrol Sci. Technol.* 4:501–16
118. Roush RT. 1998. Two-toxin strategies for management of insect resistant transgenic crops: Can pyramiding succeed where pesticide mixtures have not? *Philos. Trans. R. Soc. London Ser. B* 353:1777–86
119. Roush RT, Shelton AM. 1997. Assessing the odds: the emergence of resistance to *Bt* transgenic plants. *Nat. Biotechnol.* 15(9):5–6
120. Saxena D, Flores S, Stotzsky G. 1999. Insecticidal toxin in root exudates from *Bt* corn. *Nature* 402:480
121. Saxena D, Stotzsky G. 2001. Fate and effects of the insecticidal toxins from *Bacillus thuringiensis* in soil. *Inf. Syst. Biotechnol. News Rep.* (May)

122. Schneider JC. 1999. Confidence interval for Bayesian estimates of resistance allele frequencies. *J. Econ. Entomol.* 92:755
123. Schroeder HE, Gollasch S, Moore A, Tabe LM, Craig S, et al. 1995. Bean alpha-amylase inhibitor confers resistance to the pea weevil (*Bruchus pisorum*) in transgenic peas (*Pisum sativum* L.). *Plant Physiol.* 107:1233–39
124. Shelton AM, Roush RT. 1999. False reports and the ears of men. *Nat. Biotechnol.* 17:832
125. Shelton AM, Tang JD, Roush RT, Metz TD, Earle ED. 2000. Field tests on managing resistance to *Bt*-engineered plants. *Nat. Biotechnol.* 18:339–42
126. Shelton AM, Sears MK. 2001. The monarch controversy: scientific interpretations and public relations. *Plant J.* 27: 483–88
127. Deleted in proof
128. Shoemaker R, ed. 2001. *USDA Economic Issues in Agricultural Biotechnology*. *Agric. Inf. Bull. No. 762*. Washington, DC: US Dep. Agric. 53 pp.
129. Siegel JP. 2000. Bacteria. See Ref. 81a, pp. 209–30
130. Deleted in proof
131. Snow AA, Palma PM. 1997. Commercialization of transgenic plants: potential ecological risks. *BioScience* 47:86– 96
132. State Counc. P. R. China. 2001. Safety Administration Regulation on Agricultural Transgenic Organisms. *People's Daily*, June 7
133. Stewart CN Jr, Wheaton SK. 2001. GM crop data–agronomy and ecology in tandem. *Nat. Biotechnol.* 19:3
134. Stone TB, Sims SR. 1993. Geographic susceptibility of *Heliothis virescens* and *Helicoverpa zea* to *Bacillus thuringiensis*. *J. Econ. Entomol.* 86:989–94
135. Tabashnik BE, Patin AL, Dennehy TJ, Liu YB, Carriere Y, et al. 2000. Frequency of resistance to *Bacillus thuringiensis* in field populations of pink bollworm. *Proc. Natl. Acad. Sci. USA* 97:12980–84
136. Tang JD, Collins HL, Metz TD, Earle ED, Zhao J, et al. 2001. Greenhouse tests on resistance management of Bt transgenic plants using refuge strategies. *J. Econ. Entomol.* 94:240–47
137. Thiel PG, Marasas WFO, Sydenham EW, Shephard GS, Gelderblom WCA. 1992. The implications of naturally occurring levels of fumonisins in corn for human and animal health. *Mycopathologia* 117:3–9
138. Thompson PB. 2000. Bioethics issues in a bio-based economy. In *The Biobased Economy of the Twenty-First Century: Agriculture Expanding into Health, Energy, Chemicals, and Materials. NABC Rep. 12*. Ithaca, NY: Natl. Agric. Biotechnol. Counc. 196 pp.
139. Traynor PL, Westwood JH, eds. 1999. *Proc. Workshop Ecol. Effects Pest Resistance Genes Managed Ecosystems*, Jan. 31–Feb 3. Bethesda, MD: Blacksburg, VA: Inf. Syst. Biotechnol. 133 pp. http://www.isb.vt.edu
140. Tu JM, Zhang GA, Datta K, Xu CG, He YQ, et al. 2000. Field performance of transgenic elite commercial hybrid rice expressing *Bacillus thuringiensis* delta-endotoxin. *Nat. Biotechnol.* 18:1101–4
141. USDA Natl. Agric. Stat. Serv. (NASS). 2001. *Census of agriculture*. http://www.usda.gov/nass/
142. US EPA. 1995. Pesticide fact sheet for *Bacillus thuringiensis* susp. *kurstaki* CryI(A)b delta-endotoxin and the genetic material necessary for the production (plasmid vector pCIB4431) in corn. *EPA Publ. EPA731–F-95–004*
143. US EPA. 1999. *Cry9C Food Allergenicity Assessment Background Document*. http://www.epa.gov/pesticides/biopesticides/cry9c/cry9c-peer_review.htm
144. US EPA. 1999. *EPA and USDA Position Paper on Insect Resistance Management in Bt Crops*. 5/27/99, minor revis. 7/12/99. http://www.epa.gov/pesticides/biopesticides/btworkshop618.htm
145. US EPA, Off. Sci. Coord. Policy. FIFRA Sci. Advisory Panel. 1999. *Sets of*

scientific issues being considered by the Environmental Protection Agency. Washington, DC: US EPA

146. US EPA, Off. Pestic. Programs, Biopesticides Pollut. Prev. Div. 2000. *Biopesticides registration document; preliminary risks and benefits sections; Bacillus thuringiensis plant-pesticides*. Washington, DC: US EPA
147. US EPA 2000. *Bt cotton refuge requirements for the 2001 growing season*. http://www.epa.gov/pesticides/biopesticides/otherdocs/bt_cotton_refuge_2001.htm
148. US EPA. 2001. *Regulations Under the Federal Insecticide, Fungicide, and Rodenticide Act for Plant-Incorporated Protectants (Formerly Plant-Pesticides)*. 40 CFR Parts 152 and 174. http://www.epa.gov/scipoly/6057–7.pdf
149. US EPA. 2001. *Bt plant pesticides risk and benefit assessments. 2000 FIFRA SAP Rep. No. 200–7*. http://www. epa. gov/scipoly/sap/2000/october/octoberfinal. pdf
150. Vaeck M, Reynaerts A, Hofte H, Jansens S, Beuckeleer MD, et al. 1987. Transgenic plants protected from insect attack. *Nature* 328:33–37
151. Willams MR. 1999. *Cotton Crop Losses*. http://www.msstate.edu/Entomology/CTNLOSS/1998loss.html
152. Wolfenbarger LL, Phifer PR. 2000. The ecological risks and benefits of genetically engineered plants. *Science* 290:2088–93
153. Wolfenbarger LL, Phifer PR. 2001. GM crops and patterns of pesticide use. *Science* 292:637–38
154. World Health Organ. 2000. *Safety aspects of genetically modified foods of plant origin*. Rep. joint FAO/WHO expert consulation on foods derived from biotechnology, 29 May–2 June. http://www.who.int/fsf/GMfood/FAO-WHO_Consultation_report_2000.pdf
155. Wraight C, Zangeri AR, Carroll MJ, Berenbaum MR. 2000. Absence of toxicity of *Bacillus thuringiensis* pollen to black swallowtails under field conditions. *Proc. Natl. Acad. Sci. USA* 97:7700–3
156. Xia JY, Cui JJ, Ma LH, Dong SX, Cui XF. 1999. The role of transgenic *Bt* cotton in integrated pest management. *Acta Gossypii Sin.* 11:57–64
157. Ye GY, Shu QY, Yao HW, Cui HR, Cheng XY, et al. 2001. Field evaluation of resistance of transgenic rice containing a synthetic cry1Ab gene from *Bacillus thuringiensis* (Berliner) to two stem borers. *J. Econ. Entomol.* 94:271–76
158. Young SY, Steinkraus DC, Gouge DH. 2000. Microbial insecticide application. See Ref. 81a, pp. 467–95
159. Yu CG, Mullins M, Warren GW, Koziel MG, Estruch JJ. 1997. The *Bacillus thurigiensis* vegetative insecticidal protein Vip3A lyses midgut epithelium cells of susceptible insects. *Appl. Environ. Microbiol.* 63:532–36
160. Zhao JZ, Fan YL, Fan XL, Shi XP, Lu MG. 1999. Evaluation of transgenic tobacco expressing two insecticidal genes to delay resistance development of *Helicoverpa armigera*. *Chin. Sci. Bull.* 44:1871–73
161. Deleted in proof
162. Zhao JZ, Rui CH, Lu MG, Fan XL, Ru LJ, Meng XQ. 2000. Monitoring and management of *Helicoverpa armigera* resistance to transgenic *Bt* cotton in Northern China. *Res. Pest Manag. Newsl.* 11(1):28–31

Annual Review of Entomology
Volume 47, 2002

CONTENTS

ROSS RIVER VIRUS: ECOLOGY AND DISTRIBUTION, *Richard C. Russell* 1

BIOLOGY AND MANAGEMENT OF THE SMOKYBROWN COCKROACH, *Arthur G. Appel and Lane M. Smith II* 33

SEQUESTRATION OF DEFENSIVE SUBSTANCES FROM PLANTS BY LEPIDOPTERA, *Ritsuo Nishida* 57

REGULATION OF DIAPAUSE, *David L. Denlinger* 93

BACTERIAL SYMBIONTS OF THE TRIATOMINAE AND THEIR POTENTIAL USE IN CONTROL OF CHAGAS DISEASE TRANSMISSION, *C. Ben Beard, Celia Cordon-Rosales, and Ravi V. Durvasula* 123

STRATEGIES AND STATISTICS OF SAMPLING FOR RARE INDIVIDUALS, *Robert C. Venette, Roger D. Moon, and William D. Hutchison* 143

BIOLOGY AND MANAGEMENT OF THE JAPANESE BEETLE, *Daniel A. Potter and David W. Held* 175

BIOLOGY AND ECOLOGY OF HIGHER DIPTERA FROM FRESHWATER WETLANDS, *Joe B. Keiper, William E. Walton, and Benjamin A. Foote* 207

INVASIONS BY INSECT VECTORS OF HUMAN DISEASE, *L. Philip Lounibos* 233

OMNIVORY IN TERRESTRIAL ARTHROPODS: MIXING PLANT AND PREY DIETS, *Moshe Coll and Moshe Guershon* 267

HOW TO BE A FIG WASP, *George D. Weiblen* 299

ALTERNATIVES TO METHYL BROMIDE TREATMENTS FOR STORED-PRODUCT AND QUARANTINE INSECTS, *Paul G. Fields and Noel D. G. White* 331

ECOLOGY AND BEHAVIOR OF FIRST INSTAR LARVAL LEPIDOPTERA, *Myron P. Zalucki, Anthony R. Clarke, and Stephen B. Malcolm* 361

ARTHROPOD ALLERGENS AND HUMAN HEALTH, *Larry G. Arlian* 395

COMPETITIVE DISPLACEMENT AMONG INSECTS AND ARACHNIDS, *Stuart R. Reitz and John T. Trumble* 435

ENDOCRINE INSIGHTS INTO THE EVOLUTION OF METAMORPHOSIS IN INSECTS, *James W. Truman and Lynn M. Riddiford* 467

BIOCHEMISTRY AND GENETICS OF INSECT RESISTANCE TO *BACILLUS THURINGIENSIS*, *Juan Ferré and Jeroen Van Rie* 501

IRON METABOLISM IN INSECTS, *Helen Nichol, John H. Law, and Joy J. Winzerling* 535

CAN GENERALIST PREDATORS BE EFFECTIVE BIOCONTROL AGENTS?, *W. O. C. Symondson, K. D. Sunderland, and M. H. Greenstone* 561

ARTHROPODS ON ISLANDS: COLONIZATION, SPECIATION, AND CONSERVATION, *Rosemary G. Gillespie and George K. Roderick* 595

THE POPULATION BIOLOGY OF OAK GALL WASPS (HYMENOPTERA: CYNIPIDAE), *Graham N. Stone, Karsten Schönrogge, Rachel J. Atkinson, David Bellido, and Juli Pujade-Villar* 633

SHORT, LONG, AND BEYOND: MOLECULAR AND EMBRYOLOGICAL APPROACHES TO INSECT SEGMENTATION, *Gregory K. Davis and Nipam H. Patel* 669

BIOLOGY AND MANAGEMENT OF ECONOMICALLY IMPORTANT LEPIDOPTERAN CEREAL STEM BORERS IN AFRICA, *Rami Kfir, W. A. Overholt, Z. R. Khan, and A. Polaszek* 701

THE ECOLOGY AND EVOLUTION OF ANT ASSOCIATION IN THE LYCAENIDAE (LEPIDOPTERA), *Naomi E. Pierce, Michael F. Braby, Alan Heath, David J. Lohman, John Mathew, Douglas B. Rand, and Mark A. Travassos* 733

SYMPATRIC SPECIATION IN PHYTOPHAGOUS INSECTS: MOVING BEYOND CONTROVERSY?, *Stewart H. Berlocher and Jeffrey L. Feder* 773

HOST PLANT QUALITY AND FECUNDITY IN HERBIVOROUS INSECTS, *Caroline S. Awmack and Simon R. Leather* 817

ECONOMIC, ECOLOGICAL, FOOD SAFETY, AND SOCIAL CONSEQUENCES OF THE DEPLOYMENT OF BT TRANSGENIC PLANTS, *A. M. Shelton, J.-Z. Zhao, and R. T. Roush* 845

CONTROL AND BIOCHEMICAL NATURE OF THE ECDYSTEROIDOGENIC PATHWAY, *Lawrence I. Gilbert, Robert Rybczynski, and James T. Warren* 883

THE BIOLOGY OF THE DANCE LANGUAGE, *Fred C. Dyer* 917

INDEXES

Subject Index 951

Cumulative Index of Contributing Authors, Volumes 38–47 987

Cumulative Index of Chapter Titles, Volumes 38–47 991

ERRATA

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