ANNUAL REVIEWS

Annual Review of Entomology

Insect-Resistant Genetically Engineered Crops in China: Development, Application, and Prospects for Use

Yunhe Li,[1,*] Eric M. Hallerman,[2] Kongming Wu,[1] and Yufa Peng[1]

[1]State Key Laboratory for Biology of Plant Diseases and Insect Pests, Institute for Plant Protection, Chinese Academy of Agricultural Sciences, Beijing 100193, China; email: liyunhe@caas.cn

[2]Department of Fish and Wildlife Conservation, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061, USA

Annu. Rev. Entomol. 2020. 65:273–92

First published as a Review in Advance on October 8, 2019

The *Annual Review of Entomology* is online at ento.annualreviews.org

https://doi.org/10.1146/annurev-ento-011019-025039

*Corresponding author

Keywords

Bt cotton, *Bt* rice, *Bt* corn, ecological impacts, insect resistance

Abstract

With 20% of the world's population but just 7% of the arable land, China has invested heavily in crop biotechnology to increase agricultural productivity. We examine research on insect-resistant genetically engineered (IRGE) crops in China, including strategies to promote their sustainable use. IRGE cotton, rice, and corn lines have been developed and proven efficacious for controlling lepidopteran crop pests. Ecological impact studies have demonstrated conservation of natural enemies of crop pests and halo suppression of crop-pest populations on a local scale. Economic, social, and human health effects are largely positive and, in the case of *Bt* cotton, have proven sustainable over 20 years of commercial production. Wider adoption of IRGE crops in China is constrained by relatively limited innovation capacity, public misperception, and regulatory inaction, suggesting the need for further financial investment in innovation and greater scientific engagement with the public. The Chinese experience with *Bt* cotton might inform adoption of other *Bt* crops in China and other developing countries.

INTRODUCTION

China has more than 20% of the world's population but less than 7% of the arable land. Rapid urbanization and excessive application of pesticides and fertilizers have led to loss of arable land (69). China is dependent upon food imports and, in 2017, imported 130.6 million tons of various crops (**http://www.agrogene.cn/info-4673.shtml**). Against this background, China's central government made the strategic decision to develop and apply agricultural biotechnology to increase agricultural productivity and to promote national food security and green agricultural development (65). Since the 1980s, research and development of genetically engineered (GE) crops have received steadily increasing financial support. The Chinese government initiated the National GM Variety Development Special Program (NGSP) in 2008 with the intent of investing $3.5 billion to identify additional functional genes and to develop new GE varieties, improving the level of research and industrialization of agricultural GE organisms (69). Great progress has been made in the development of insect-resistant GE (IRGE) crops, especially cotton, rice, and corn.

We examine the current status of research and application of IRGE crops in China, analyze the prospects and challenges, and discuss strategies to promote the development and application of GE crop technology in China. The Chinese experience with *Bt* cotton (i.e., cotton plants modified to produce one or more endotoxins derived from the bacterium *Bacillus thuringiensis*) should provide valuable lessons in sustainable use of a wide range of *Bt* crops for other countries, in particular developing countries with agricultural situations similar to China's.

DEVELOPMENT OF INSECT-RESISTANT GENETICALLY ENGINEERED CROPS IN CHINA

In China, cotton is an important cash crop, and rice and corn are important cereal crops (59, 61, 66). Cotton is now mainly planted in Xinjiang Province, while rice and corn are grown in most provinces. All of these crops suffer severe damage from many insect pests, with lepidopteran species being the most damaging (16, 33, 59, 124). Management of these pests once relied primarily on chemical insecticides, resulting in environmental and human health problems (16, 18, 25, 38).

Insect-Resistant Genetically Engineered Cotton

Over 300 herbivorous insect species have been recorded in Chinese cotton fields (124), including the lepidopterans cotton bollworm (*Helicoverpa armigera*), pink bollworm (*Pectinophora gossypiella*), corn borer (*Ostrinia furnacalis*), beet armyworm (*Spodoptera exigua*), common cutworm (*Spodoptera litura*), spiny bollworm (*Earias cupreoviridis*), and cotton looper (*Anomis flava*). Outbreaks of cotton bollworm alone have caused huge economic losses and resulted in overuse and misuse of chemical insecticides (18, 38).

Research on IRGE cotton in China started in the early 1990s. The first IRGE cotton event, produced in 1994 for experimental use, expressed a *cry1Ac/cry1Ab* fusion gene and exhibited cotton bollworm control efficacy of over 80% (138). Subsequently, stacked cotton events (i.e., plant lines resulting from an insertion of a transgene into a specific genomic location) expressing *Bt* and *CpTI* (cowpea trypsin inhibitor) or *GNA* (*Galanthus nivalis* agglutinin) were developed for delaying Bt resistance among target pests or for controlling additional insect pests such as aphids (67) (**Supplemental Table 1**). In recent years, new types of IRGE cotton events have been obtained using RNA interference (RNAi) technology or RNAi pyramided with *Bt* genes (76, 77, 88, 127) (**Supplemental Table 1**). Ni et al. (88) reported that pyramided cotton expressing a Bt protein and dsRNA not only provided excellent control of target pests, but also substantially delayed resistance

Supplemental Material >

relative to using Bt alone. Among IRGE crops, only *Bt* cotton is in commercial production in China today.

Insect-Resistant Genetically Engineered Rice

In Chinese rice ecosystems, there are three major lepidopteran pests, the rice striped stem borer (*Chilo suppressalis*), yellow stem borer (*Scirpophaga incertulas*), and rice leaf roller (*Cnaphalocrocis medinalis*) (16), which cause severe yield losses (59). Rice stem borers are especially damaging, annually causing losses of about 11.5 billion renminbi (RMB) ($1.8 billion) (107).

The majority of *Bt* rice events developed in China were designed for controlling lepidopteran pests by expressing *cry1*, *cry2*, or *cry9* genes (66). Some IRGE rice lines express fusion genes such as *cry1Ab/cry1Ac*, *cry1Ab/vip3H*, or *cry1Ac/cry1-like*, and others express pyramided *cry1Ac* and *CpTI* genes (**Supplemental Table 1**). RNAi technology also has been used in the development of IRGE rice. Some rice lines express microRNAs such as *Csu-novel-miR15* to confer resistance to the rice stem borer (48).

Supplemental Material >

Insect-Resistant Genetically Engineered Corn

Among multiple insect pests on corn, the lepidopteran pests *O. furnacalis*, *H. armigera*, and *Mythimna separata* are the most serious, causing approximately 10% yield loss in spring corn, 20–30% in summer corn, and over 30% with heavy infestations, resulting in huge economic losses in China (66).

Current *Bt* corn lines in China mainly express *cry1Ab*, *cry1Ac*, *cry1Ie*, *cry1Ah*, *cry1C*, or *cry2* genes, with some expressing genes that are modified from *cry1Ab* and *cry1Ia1* (*cryFLIa*) or *cry1Ac* (*mCry1Ac* and *cry1AcM*). There have also been some IRGE corn lines that express fusion genes such as *cry1Ab/2Aj*, *cry1Ab/vip3DA*, and *cry1Ah/cry1Ie* (**Supplemental Table 1**).

INSECT-RESISTANT GENETICALLY ENGINEERED CROPS IN COMMERCIAL USE IN CHINA: *Bt* COTTON

History of Commercial Cultivation

Bt cotton was approved for commercialization in China in 1997. In the first year, <0.1 million ha of *Bt* cotton was planted. Since then, the area planted has expanded rapidly, especially in the Yellow River region and the Changjiang River region (CRR) (124). Planting reached 3.9 million ha in 2007 and remained relatively stable at approximately 4.0 million ha through 2015 (61). The area planted to cotton in China decreased to 2.9 million ha in 2016 and 2017 due to change of policy affecting the structure of the sector (46). The *Bt* cotton lines that are currently being planted in China express *cry1Ac*, *cry1Ab/Ac*, or *cry1A+CpTI* genes targeting lepidopteran pests (61).

Regional Suppression of Target Pests

The major target pest of *Bt* cotton is cotton bollworm (*H. armigera*), a polyphagous species feeding on over 200 species of host plants, including cotton, corn, soybean, peanut, and vegetable crops in China (126). Large-scale, long-term field monitoring shows that, with increasing adoption of *Bt* cotton, cotton bollworm populations have been effectively suppressed not only on cotton, but also on non-*Bt* host crops, including corn, soybean, peanut, and vegetables in areas near plantings of *Bt* cotton (126). In China, wheat is the main host crop for first-generation *H. armigera* larvae, and cotton is usually the main host for egg deposition by moths of the first generation, acting as the source of subsequent generations on other crops (126). With wide adoption of *Bt* cotton,

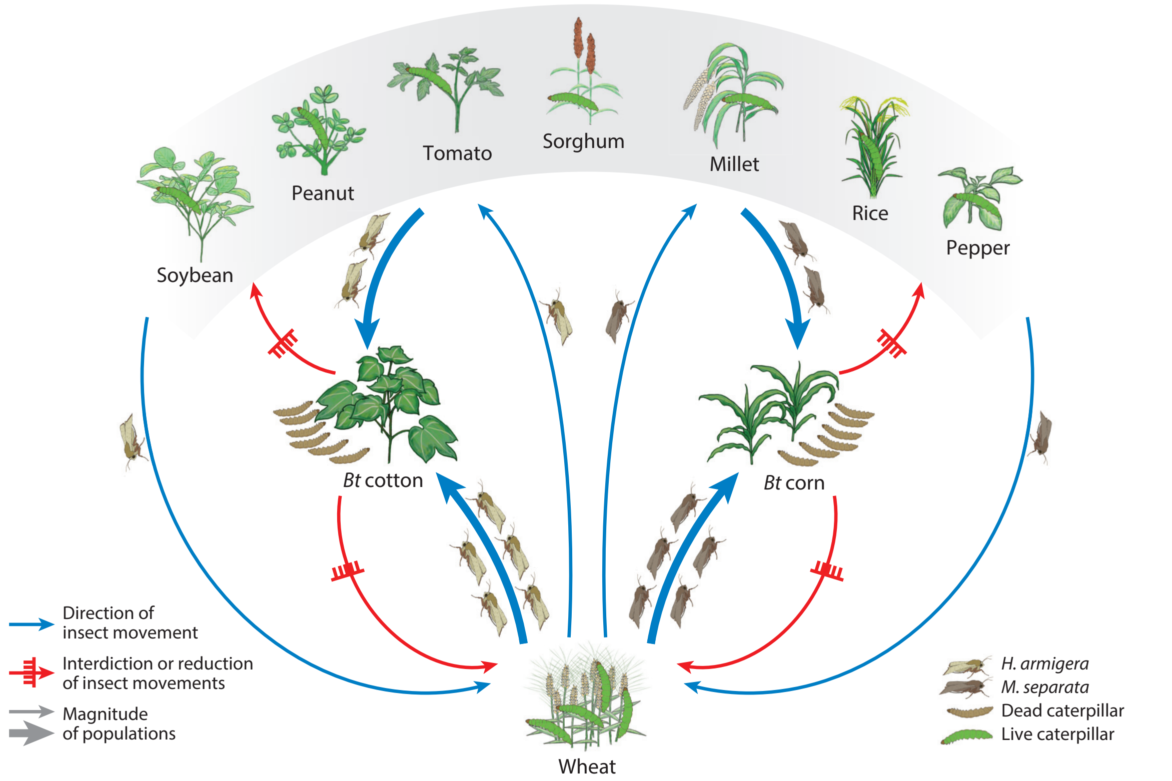

Figure 1

Suppression of populations of *Helicoverpa armigera* and *Mythimna separata* not only on *Bt* crops, but also on non-*Bt* host crops with wide adoption of *Bt* cotton and *Bt* corn.

most offspring of first-generation *H. armigera* are killed in cotton fields, significantly reducing the production of subsequent generations on other host crops; *Bt* cotton thereby controls cotton bollworm populations across wide planting areas (**Figure 1**) (106). Pink bollworm (*P. gossypiella*), is another major insect pest on cotton, mainly in the CRR (115). Because cotton is the sole host plant for this species, analysis of 16 years of field-survey data indicated that increased cultivation of *Bt* cotton significantly decreased the population density of pink bollworm not only on *Bt* cotton, but also on non-*Bt* cotton in the CRR (43, 114). Modeling analyses have suggested that as the percentage of *Bt* cotton increases, it contributes progressively less to decrease of pink bollworm density (43). Nonetheless, the ecological benefits of *Bt* cotton accrue not only to *Bt* cotton farmers, but also to growers of other target pest host crops (61, 96). Such an effect was also reported recently for *Bt* corn in the United States, where widespread adoption suppresses pests regionally, resulting in marked decreases in insecticide application and damage to vegetable crops (23).

Different lepidopteran species exhibit significantly different susceptibility to the Cry proteins produced by *Bt* cotton (85). For example, *Bt* cotton planted in China has limited activity against the beet armyworm (*S. exigua*) (141) and common cutworm (*S. litura*) (116, 132), and these insects may become major pests in *Bt* cotton fields; thus, an alternative strategy is required for controlling these pests (116). Cotton lines expressing both Cry1Ac and Cry2Ab seem to be promising options (3).

Ecological Issues Associated with Planting of *Bt* Cotton

Evolution of resistance in target pests. Over 20 years of experience planting IRGE crops suggests that evolution of resistance by target pests is the major threat to sustainable use (11, 30, 58, 86, 112, 113). Since the appearance of IRGE crops, resistance to *Bt* has elicited concern in the scientific community and the public, and multiple strategies have been developed to prevent or delay development of *Bt*-resistant insect populations (28, 30, 89). The most effective strategy has proven to be the combination of high expression of Bt proteins and deployment of refuges (28, 89). The refuge approach permits a fraction of the population to escape selection by Bt proteins; these surviving susceptible insects are expected to mate with any resistant ones that survived exposure to Bt proteins to produce Bt-susceptible, heterozygous offspring, presuming that the resistance trait has a recessive mode of phenotypic expression (28, 58, 112). The high dose of Bt protein produced by the *Bt* plants is assumed to kill all or nearly all heterozygous target insects (37, 58).

The high-dose and refuge strategy has been applied worldwide to delay insect pest resistance to *Bt* crops (112). The refuges are generally structured, i.e., the farmers are mandated to plant a specified proportion of a non-*Bt* variety as a refuge for susceptible target pests adjacent to the *Bt*-expressing IRGE crop (37, 58). The strategy is well deployed in the United States and Australia and has proven successful in substantially delaying pest resistance to *Bt* crops (37, 112). However, the structured refuge is difficult to implement in countries with small-scale farms and millions of individual growers, such as China, India, and many other Asian and African countries, because of the challenges associated with educating and monitoring so many farmers (60, 122). For example, the Indian government required farmers to plant a non-*Bt* cotton hybrid or pigeon pea as a refuge around *Bt* cotton fields (37). However, field resistance of the target pest *P. gossypiella* emerged just seven years after commercialization of *Bt* cotton in India, which was attributed to use of illegal *Bt* cotton seeds with low doses of Bt protein and noncompliance with the refuge strategy (37).

Because of the small-scale farming system, the structured refuge has not been required for *Bt* cotton in China (51). However, the frequency of resistance to Cry1Ac in *H. armigera* is still low, and *Bt* cotton producing Cry1Ac has maintained substantial control of this pest in China (51). This success relies on the presence of many other host crops—such as corn, soybean, peanut, and vegetables—serving as natural refuges to produce susceptible cotton bollworm individuals (51, 58, 122, 123, 125), although modeling predictions suggest that they are not as effective as an equivalent area of non-*Bt* cotton refuge (51). The success of the natural refuge strategy in China is attributed to *H. armigera* being (*a*) a polyphagous pest infesting multiple host crop species that overlap in space and time in China and (*b*) a highly mobile pest, with high gene flow among populations from different host crops (51, 58, 122, 124, 126).

As noted, the refuge strategy is premised on a recessive mode of expression of resistance in the target pest (58). However, field populations of *H. armigera* in China have also shown non-recessive resistance, and the percentage of individuals with non-recessive expression of resistance has increased rapidly (51, 137). This may suggest that the natural refuge strategy will gradually lose its efficacy in delaying resistance of *H. armigera* to *Bt* cotton. Development of *Bt* cotton producing two or more Bt proteins with limited or no cross-resistance has been suggested for slowing further increase in Bt resistance in cotton bollworm (51).

In contrast to *H. armigera*, pink bollworm (*P. gossypiella*) is an oligophagous insect, feeding almost exclusively on cotton in China (114). The natural refuge strategy therefore is not applicable (58). Thus, with increasing adoption of *Bt* cotton, pink bollworm would quickly lose its non-*Bt* refuge. Based on resistance monitoring, Wan et al. (114) predicted that resistance of pink bollworms to Cry1Ac cotton would rapidly increase after 2010, with further decrease of non-*Bt* cotton production. This phenomenon has not emerged, and it was unexpectedly found that the percentage of field populations with one or more larvae surviving at the diagnostic concentration declined from 56% in 2008–2010 to 0% in 2011–2015 (117). The unexpected decline of resistance was attributed to the cotton seeds planted since 2010 being F_2 hybrids (117). Production of F_1 hybrid seeds needs costly hand-pollination; to reduce costs, seed producers had crossed *Bt* cotton with non-*Bt* cotton to create F_1 hybrids. Self-pollination of F_1 hybrids produced F_2 hybrid seeds, resulting in sale of seed lots consisting of 25% *Bt* homozygotes, 50% *Bt* hemizygotes, and 25% non-*Bt* homozygotes expressing no Cry protein (117). The resulting *Bt* and non-*Bt* seed mixture boosted the percentage of non-*Bt* cotton plants in the CRR of China serving as refuges for pink bollworms, and development of resistance to *Bt* cotton was reversed (117).

Outbreaks of nontarget secondary pests. The currently used Cry proteins are highly specific to target pests; thus, nontarget secondary insect pest populations may increase because they are not susceptible to Bt proteins. Such insects would have been controlled by broad-spectrum chemical insecticides applied before the introduction of *Bt* crops (14, 75, 86, 94). In China, mirid bugs (Heteroptera: Miridae) were first recorded on cotton during the early 1930s and were regarded as secondary pests (73). With wide-scale adoption of *Bt* cotton, mirid bug populations have progressively increased and acquired pest status in cotton and other host crops (75, 140). Lu et al.'s (75) analyses showed that mirid population increase was associated with reduced insecticide application in this crop after introduction of *Bt* cotton; that is, mirids had been controlled by insecticide used mainly for controlling cotton bollworms.

Despite the increase of mirid populations, a summary assessment suggested that the effects of secondary insect pests on *Bt* cotton were minor in comparison to the effect of a decrease in major insect pests and insecticide use, suggesting that the benefit of *Bt* cotton cultivation is sustainable in China (94, 96). The effects of secondary insect pests associated with *Bt* crops have been discussed globally; in general, authors conclude that the issue of secondary insect pests is not sufficient to undermine the use of *Bt* crops but should be attended to, and that necessary measures should be taken to sustain use of this technology (14, 73). In China, scientists have been developing and applying various measures, such as cultural control, biological control, trap-cropping, chemical control, and other approaches, to manage mirid bugs in *Bt* cotton; thus, mirid bugs may not prove sufficiently problematic to affect sustainable use of *Bt* cotton in China (71, 72).

Ecological Benefits Associated with Planting of *Bt* Cotton

Cotton supports large and diverse communities of natural enemies of arthropods, which play an important role in suppression of cotton insect pests (85). Therefore, potential effects of IRGE crops on natural enemies and other beneficial species have drawn much attention worldwide (26, 27, 90, 99–101). Extensive studies showed that Cry proteins produced by commercialized *Bt* crops are highly specific and have no direct toxicity to nontarget organisms, including arthropod natural enemies (62, 86). Instead, cultivation of *Bt* cotton can significantly reduce the application of insecticides and has therefore created significant opportunities for conservation of natural enemies, enhancing biological control in the cotton agroecosystem (74, 84, 85). Long-term monitoring of the ecological effects in China suggests that reduced insecticide spraying due to adoption of *Bt* cotton has favored a marked increase of the generalist natural enemies and promoted their biocontrol services—in particular, suppressing the abundance of aphid pests (74, 140). Moreover, generalist predators usually have strong dispersal ability, such that increasing predator abundance on *Bt* cotton ultimately promoted predator-meditated biocontrol services across the agroecosystem of China (74).

Social and Economic Effects of Planting *Bt* Cotton

Because IRGE crops were developed to kill agricultural pests, their impacts go beyond ecological considerations to include economic and social impacts. A growing literature shows that Chinese smallholder farmers have benefited economically from production of *Bt* cotton. Farm budget data from 300–400 farmers in five provinces from 1999 to 2001 showed complex changes in crop yields and pesticide use (41, 91); for example, yields were 9% higher and insecticide applications 71% lower in Shandong Province. Farmers realized positive net income from adoption of *Bt* cotton, mainly through reduced input and labor costs (38). Qiao (94) showed that the economic benefit of *Bt* cotton was maintained from 1997 to 2012; farmers saved 4.12 billion RMB on pesticide use and 8.70 billion RMB on labor. The benefit from the increase in yield was even higher. Widespread use of *Bt* cotton in China suppressed the density of the pest population regionally, yielding benefits to both adopters and non-adopters (96, 97, 126). The average yield gain of *Bt* cotton in China was 10%, and the aggregate income benefit was more than $19.6 billion from 1997 to 2016 (9).

In addition to direct economic benefits, indirect benefits of increased employment, household income, and reduced poverty have been shown in other countries (98), although the socioeconomic impacts vary with local farming practices (105, 110).

A survey of cotton farmers in northern China in 1999–2001 showed that reduced pesticide use following adoption of *Bt* cotton adoption led to decreased incidence of acute poisoning (35). Positive impacts of *Bt* cotton on the health of farmers also have been observed in Pakistan (2) and India (52).

INSECT-RESISTANT GENETICALLY ENGINEERED CROPS IN THE PIPELINE

Two *Bt* rice lines, *Bt* Shanyou 63 and Huahui No. 1, were awarded biosafety certificates in China in 2009, and Huahui No. 1 has been approved for consumption by the US Food and Drug Administration, but the lines have not yet been approved for agricultural production in China. This may be attributable to a low level of understanding and acceptance of GE crops by Chinese consumers (59). The thirteenth Five-Year Plan for Science and Technology Development, issued in 2016 by the State Council of China, aimed to accelerate development and application of GE crops, with priority placed on commercializing corn, cotton, and soybean (60). *Bt* corn may soon be approved for commercialization (129). In this section, we analyze potential advantages and safety concerns and discuss the prospects for improving agricultural productivity and social and economic effects with adoption of *Bt* rice and corn in China.

Potential Advantages

High efficiency in regional target pest control. Extensive studies have been conducted to evaluate the efficacy of *Bt* rice and corn lines against target pests in China, including *C. suppressalis*, *S. incertulas*, and *C. medinalis* on rice and *O. furnacalis*, *H. armigera*, and *M. separata* on corn. Liu et al. (66) showed that several *Bt* rice and corn lines exhibit efficient control of major target lepidopteran pests. For example, the *Bt* rice lines mfb-MH86 (producing Cry1Ab), T1C-19 (Cry1C), and Huahui No. 1 (Cry1Ab/1Ac) exhibit high and relatively consistent pest resistance throughout the growing season (66). The Shuangkang 12–5 corn line expressing *cry1Ab/2Aj* can provide almost 100% control of *C. medinalis* (66).

As discussed above, widespread adoption of *Bt* crops can regionally suppress target pest populations, benefiting not only the *Bt* crop, but also non-*Bt* crops (23, 44, 126). The target species for *Bt* corn, *O. furnacalis* and *M. separata*, are similar to *H. armigera* in terms of feeding not only on corn, but also on other crop species, including millet, sorghum, soybean, and many vegetables in China (135). Thus, area-wide planting of *Bt* corn may benefit not only corn producers, but also other crop producers by regional suppression of the target pest populations, as was observed with *Bt* cotton in China (126) (**Figure 1**) and *Bt* corn in the United States (23). Especially since wheat is the host for first-generation *H. armigera* and *M. separata*, suppression of their populations by *Bt* cotton and *Bt* corn will minimize damage from these pests to wheat, a staple crop in north-central China (**Figure 1**). Compared to *O. furnacalis*, *H. armigera*, and *M. separata*, the target pests of *Bt* rice have relatively few host crops, mainly feeding on rice. While *C. suppressalis* can also feed on corn, wild rice shoots, sugarcane, and other graminaceous crops (64), widespread adoption of *Bt* rice may protect these crops against this pest. Interestingly, a recent study showed that *Bt* rice could act as a dead-end trap crop for *C. suppressalis*, and thereby protect neighboring non-*Bt* rice plants, because *C. suppressalis* females prefer to lay eggs on relatively healthy *Bt* rice plants rather than on non-*Bt* rice plants that are heavily damaged by larvae of this species (50).

Both *M. separata* and *C. medinalis* are long-distance migratory pests in Asia. Commercial cultivation of *Bt* corn and rice may suppress populations of these two species not only in China, but also in neighboring countries. Outbreaks of *M. separata* in Korea and Japan are initiated mainly by immigrants from the Shandong, Hebei, Liaoning, and Jilin Provinces of China (34, 53) (**Figure 2**). Because both corn and rice are main host crops of *M. separata* (49), wide adoption of *Bt* corn and rice in China might be expected to significantly reduce migration of this species to Japan and Korea (**Figure 2**). *C. medinalis* has weak tolerance of cold temperatures and cannot overwinter successfully north of 30°N latitude (142). Very low densities of *C. medinalis* overwinter in southern China; most *C. medinalis* migrate from Southeast Asia in March and April (93, 118, 142) (**Figure 2**). Thus, if *Bt* rice is commercially grown in Yunnan, Guangxi, Guangdong and Hainan Provinces, *C. medinalis* populations would be expected to decrease not only there, but also in other rice-growing areas in China. Meanwhile, because of decreased southward migration in fall, overwintering populations may decrease in Southeast Asian countries (**Figure 2**). In addition, fall armyworm (*Spodoptera frugiperda*) first invaded China in early 2019 and spread rapidly. Because of its resistance to multiple pesticides, it is challenging to control this corn pest (55). The planting of *Bt* corn in China may prove an important strategy for controlling the pest and may prevent its spread to Japan and Korea.

Ecological benefits. The potential for adverse effects on valued nontarget organisms has been a key concern associated with the production of IRGE crops (63, 99). Reviews of results from numerous studies suggest that the insecticidal proteins produced by *Bt* corn and cotton have a very narrow spectrum of activity, and that planting *Bt* crops poses a negligible risk to nontarget species (27, 45, 62, 78, 87, 100, 121). The *Bt* corn and rice lines developed in China express the same or modestly modified insecticidal proteins as those produced by widely commercialized *Bt* maize and cotton lines, and extensive studies have been conducted in China that further confirm no risk to nontarget species (16, 22, 56, 59, 133).

Instead, adoption of *Bt* crops will reduce the application of synthetic insecticides and in turn provide a clear ecological benefit through reduction of unintended effects on valued nontarget species, such as natural enemies, caused by these synthetic insecticides (59, 74, 78, 121). It was estimated that commercialization of *Bt* rice in China might lead to an over 60% reduction in chemical insecticide application (39, 40, 95). By systematic analysis of the existing data, the US National Academies of Sciences, Engineering, and Medicine (NASEM) (86) reached the general conclusion that growing *Bt* crops tends to result in higher arthropod biodiversity than growing corresponding non-*Bt* crops treated with synthetic insecticides.

Figure 2

Annual population migrations of *Cnaphalocrocis medinalis* and *Mythimna separata*, showing how adoption of *Bt* rice and corn in China could serve as a barrier for immigration and suppress the populations of these two major crop pests in China and neighboring countries. Figure based on data and figures from Zhang et al. (142), Wang et al. (118), Qi et al. (93), Lee & Uhm (53) and Hirai (34).

Quality improvement for food and feed. Pest damage directly causes crop yield losses and also indirectly decreases the quality of cereals as food and feed (82, 120). For example, fungal diseases, such as *Fusarium* spp., often enter the corn plant and cause ear rot through the feeding wounds caused by insects (108). Infestation by *Fusarium* spp., such as *Fusarium verticillioides* and *Fusarium proliferatum*, can result in corn grain contamination by mycotoxins such as fumonisins and zearalenone that are produced by the fungi, which can lead to acute and chronic toxicity to humans and livestock (1, 82). Adoption of *Bt* corn can significantly reduce the damage by lepidopteran target pests and thereby reduce the opportunities for ear-rot infestation. *Bt* corn showed concentrations of fumonisins and zearalenone that were decreased by 90% and 50%, respectively, compared to unsprayed conventional corn in France (29). *O. furnacalis* and *H. armigera* damage of corn kernels is the major cause of corn ear rot in China (109, 120, 128). Therefore, *Bt* corn production in China would undoubtedly improve the food and feed safety by reducing mycotoxin contamination of corn grains.

Another major issue affecting food and feed quality is pesticide residues, posing hazards to humans via direct consumption of foods with toxic residues (5, 6, 57) or indirect consumption of meat or milk products of animals that consumed feeds with such residues (83). In conventional crop systems, pesticides are major inputs for increasing the agricultural productivity of crops. On a global scale, from 1996 to 2015, commercial production of *Bt* corn and cotton led to reductions of 53.3% and 29.1%, respectively, in the use of insecticidal active ingredients (8).

Ecological Concerns Associated with Growing *Bt* Rice and *Bt* Corn

Based on the experience of over 20 years of commercial production of *Bt* crops, the associated ecological concerns mainly comprise three aspects: evolution of Bt resistance in target pests, secondary insect pest outbreak, and gene flow.

Evolution of Bt resistance. Fundamental research has been conducted in China to develop sound strategies for managing insect resistance to *Bt* corn and rice (32). First, the baseline susceptibilities of major target pests of *Bt* corn and rice to different Bt proteins have been investigated (32). The results showed that different populations of *O. furnacalis*, *C. suppressalis*, and *C. medinalis* exhibited wide variation in susceptibility to Cry1Ab or Cry1Ac toxins, suggesting that the genetic diversity necessary for evolution of insect resistance does exist (32). Second, Bt-resistant strains of *O. furnacalis* and *C. suppressalis*, two major target pests, have been established by laboratory artificial selection (54, 130, 139). *O. furnacalis* strains with resistance to Cry1Ab or Cry1Ac have high cross-resistance to Cry1Ah, minor cross-resistance to Cry1Fa, and no cross-resistance to Cry1Ie (130, 139, 143). Cry1Ac-resistant *C. suppressalis* exhibits cross-resistance to Cry1Ab, but not to Cry1Ca and Cry2Aa (32). These findings suggest that *cry1Ie* (for control of *O. furnacalis*) and both *cry1Ca* and *cry2A* (for control of *C. suppressalis*) are ideal candidate genes for stacking with *cry1A* genes for development of pyramided *Bt* corn or rice, which may be an optimal strategy for delaying Bt resistance of the two species (32).

Since *O. furnacalis* and *M. separata* are polyphagous species as *H. armigera*, the natural refuge strategy may work well for delaying the development of resistance to *Bt* corn in these species after commercialization, especially for *M. separata*, a species with high mobility, based on the experience with *H. armigera* on *Bt* cotton (58). *C. suppressalis* and *S. incertulas* have relatively high specialization in host use, although wild rice shoots are also optimal host plants for *C. suppressalis*. Research has indicated that individuals of each of the two pests from the two crop species have partial barriers in reproduction (134), and that the area of occurrence of wild rice shoots is very limited relative to that for cultivated rice; thus, wild rice shoots are unlikely to serve as effective refuges for *C. suppressalis*. Refuge in the bag, i.e., creating a mixture of *Bt* plants and non-*Bt* plants growing side by side within fields, has delayed evolution of resistance to *Bt* corn in the United States since 2010 (79). Since this strategy has the advantage of reducing problems with farmers' noncompliance with structured refuge requirements (12, 131), it seems a promising approach for delaying Bt resistance evolution of *C. suppressalis* and *S. incertulas* with cultivation of *Bt* rice, but studies are needed focusing on larval movement between *Bt* and non-*Bt* plants, the key factor affecting the efficacy of this strategy (12). *C. medinalis* is also an oligotrophic pest, and since the majority of individuals occurring in China originally migrate from Southeast Asian countries (**Figure 2**), development of resistance of this species to *Bt* rice may not prove problematic if *Bt* rice is not adopted by neighboring countries.

Secondary insect pest outbreaks. Because corn has a narrower pest spectrum than cotton, and insecticide input in conventional corn is generally lower than in cotton, secondary pest problems related to the production of *Bt* corn seem less serious than those for *Bt* cotton (80). The most problematic secondary pest associated with *Bt* corn production is the western bean cutworm (*Striacosta albicosta*), which causes significant economic damage in the United States due to nonlethal Bt proteins produced by *Bt* corn (24, 81). So far, no study has investigated the potential for secondary insect pest outbreak should *Bt* corn be commercially grown in China. However, since rice has a wide pest spectrum, and a large amount of insecticide is applied to conventional rice for insect pest control (16), secondary pest outbreak may be a serious problem should *Bt* rice be commercialized in China (20, 119). Much attention has been paid to nontarget pests—i.e., rice planthoppers such as *Nilaparvata lugens* and *Sogatella furcifera*—since they are serious pests on rice and have exhibited frequent outbreaks in China following the adoption of hybrid rice cultivars in the 1980s (16, 119). Field surveys, however, indicated that planthoppers unexpectedly migrated from *Bt* rice fields to adjacent non-*Bt* rice fields, resulting in low densities in *Bt* rice fields (17, 20). One mechanism underlying this phenomenon is, as indicated by a study by Wang et al. (119), that low caterpillar damage in *Bt* rice fields retained low numbers of planthoppers; *N. lugens* exhibits a strong preference for caterpillar-damaged plants, which facilitates planthopper movement from undamaged *Bt* rice to caterpillar-damaged non-*Bt* rice (119). However, much more research is required to assess whether rice planthopper populations will increase or decrease after introduction of *Bt* rice, since population dynamics of arthropods is affected by multiple biotic and abiotic factors (119). Once *Bt* corn or rice is commercialized in China, large-scale, long-term field surveys should be conducted to monitor the population dynamics of key nontarget insect pests, so that practical and economically viable risk-control strategies can be developed in a timely fashion.

Gene flow and ecological consequences. Gene flow via pollen from GE crops to other sexually compatible species has been debated since the introduction of GE crops. The major concerns are that gene flow might increase the weediness of related species or impact genetic resources when a GE crop is released in an area with related native species (86). Since China is not the center of origin for corn, and there are no closely related species, only a few studies have been conducted to investigate gene flow from GE to non-GE corn cultivars (36). The maximum threshold distances with gene-flow frequencies of 1% and 0.1% were 49 m and 125 m, respectively, in the spring corn-growing region of northeast China (36); these results suggest that a requirement of 300 m separation between GE and non-GE corn is sufficient for minimizing adventitious contamination of conventional corn products by GE traits (36).

Since China has centers of origin for rice, and since weedy rice (*Oryza sativa* f. *spontanea*) and common wild rice (*Oryza rufipogon*) are widely distributed in rice-producing regions (47), many studies have investigated gene flow from GE rice to conventional rice (59). As rice is primarily self-pollinating, gene-flow frequencies from GE rice to conventional cultivars are expected to be low (70); the maximum average frequency reported was 0.875%, and was 0% when the distance reached 7 m (102–104, 136). However, gene flow from cultivars to common wild rice was very high, with the highest recorded frequency being 11.24% in Sanya (Hainan Province) and 18% in Guangzhou (Guangdong Province) (47). The maximum distances (and frequencies) of transgene flow from GE rice to wild rice were 50 m (0.076%) and 250 m (0.008%) in Guangzhou and Sanya, respectively (47). Although there was a high frequency of gene flow between cultivated rice and common wild rice, a 12-year study indicated that the F_1 hybrids of GE rice and common wild rice would gradually disappear within 3–5 years, and it was inferred that the common wild rice *O. rufipogon* may have a strong reproductive isolation mechanism (47). The gene-flow frequency from GE rice to weedy rice ranged from 0.011% to 0.046% (15). Based on these findings, it was concluded that introgression and persistence of transgenes in common wild rice populations are unlikely, the ecological risk of exogenous gene flow from GE rice to wild and weedy rice populations seems to be limited, and gene flow can be controlled by separation in space and time of flowering (47, 59). Any future commercialization of Bt rice should include large-scale monitoring of gene flow into cultivated rice relatives.

Prospects for Improving Agricultural Productivity and Social and Economic Benefits

Eight IRGE crops, including corn, cotton, eggplant, potato, rice, soybean, sugarcane, and tomato, collectively 289 events, have been approved for cultivation by regulatory authorities in 37 countries and the European Union (**http://www.isaaa.org/gmapprovaldatabase/default.asp**). The direct benefit of these IRGE crops is improvement of yield and farm profitability. Carpenter (10) summarized 49 peer-reviewed reports addressing yield or other indicators of the economic performance of GE crops, including IRGE crops. While there was variation among years, countries, and lines, increases in yield were greatest for farmers in developing countries, ranging from 16% for IRGE corn to 30% for IRGE cotton. In China and South Africa, small, resource-poor farmers benefited most. Increases in yield were smaller in developed countries.

Positive impacts on yield from production of IRGE crops have been realized in all user countries except for IRGE cotton in Australia (9). The average increase in yield across the total area planted to these traits between 1996 and 2014 was +11.7% for corn and +17% for cotton (7). The greatest improvement in yields occurred in developing countries, where conventional methods of pest control typically have been least effective (9). In developed countries, benefits accrued to cost savings associated with reduced insecticide use (8). These effects led to farm income gains. At the aggregate level, cumulatively from 1996 to 2016, the global farm income gains from using IRGE crops were $50.6 billion for IRGE corn and $54 billion for IRGE cotton (9). It was estimated that commercialization of IRGE corn in China would result in an annual increase in corn production ranging from 2.4% to 7.7% by 2025 if no corn tariff rate quota is imposed (129). An analysis of the data collected from farm households shows that adoption of IRGE rice would lead to an increase in yield of 5% and the total benefit could be as high as $6.3 billion per year (95).

Within the context of a favorable regulatory framework, IRGE crops can contribute to global food security and poverty reduction (92). The magnitude of socioeconomic benefits from IRGE crops will depend on local farming practices (98). NASEM (86) concluded that the questions of what the benefits of genetic engineering are and how they relate to the size of farmer land holding need to be examined in more detail.

By reducing the number of pesticide applications, adoption of IRGE crops has led to improvement of farmer health. As mentioned above, reduced use of insecticide on IRGE cotton in China resulted in fewer cases of pesticide toxicity (35, 41, 91). In farm-level production trials, Chinese farm households adopting IRGE rice lines reported no adverse health effects, compared to 3.0–10.9% reporting adverse health effects among similar households planting non-IRGE rice lines and using higher input of pesticides (40). Adoption of IRGE crops will not only lead to decreased incidence of acute poisoning (35), but also reduce adverse impacts on farmers' neurological, hematological, and electrolyte systems (39). NASEM (86) provides a thorough review of socioeconomic impacts of GE crops. Our interpretation of the body of work on economic, social, and health impacts collectively is that the benefits explain the rapid adoption of IRGE crop technology in countries where such lines have been approved.

BOTTLENECKS LIMITING ADOPTION IN CHINA AND DEVELOPING COUNTRIES

The mostly positive ecological, economic, and social effects of IRGE crops raise the question of why they have not been accepted more broadly in China and developing countries. Technical capacity, industry structure, public policy, and socioeconomic and international trade issues explain the lag in acceptance.

Technical Capacity

After over 20 years of effort, China has formed an integrated system of research and development from gene cloning to plant breeding to industrialization (59). However, the original innovation capacity of China in genetic engineering is still weak compared to that in developed countries such as the United States. By virtue of technological superiority, developed countries have led innovation in the development of core GE technology and utilization of functional genes (111). Within this context, fears have been raised that, with commercialization of GE crops, China may fall into a foreign patent trap, threating China's food security, food prices, farmers' livelihoods, and sovereignty (65).

Industrial Structure

Investment flows in research and development in developed countries come from both government competitive grant programs, especially for upstream, conceptual research, and the private sector, especially for development of production lines, regulatory compliance, scale-up for commercial sales, and promotion. In China and most developing countries, innovations in biotechnology are mainly realized in government-funded universities or agricultural research institutes; such entities lack access to the venture capital, regulatory compliance support, and marketing infrastructure of large multinational life sciences companies (13). The lack of close integration between universities or research institutes and biotech companies results in a commercialization lag for GE crops that further discourages companies' initiative in development and application of GE crops. This situation seriously affects the national competitiveness of the domestic GE crop industry and limits the access of developing countries to the benefits of GE technology.

Policy and Regulatory Capacity

Sustainable use of GE crops will require adoption of risk management practices to avoid or limit the potential adverse effects on the environment and human health. Such risk management is overseen by national regulatory authorities. The establishment of functional regulatory systems with the necessary scientific capacity is problematic in many developing countries (4, 98), hindering wider adoption of GE crops. Regulatory costs limit the number of GE crops that progress to adoption in particular countries, and the delay in the introduction of such crops may result in large opportunity costs (13, 92, 98).

Societal Acceptance

Largely due to low public acceptance, the pace of commercialization of GE crops has been slow, both in China (19) and globally. Low public acceptance often results from misinformation, leading to excessive and sometimes irrational concern over the safety of GE food (21, 42, 59) (**Supplemental Sidebar**). Results of a survey by Cui & Shoemaker (21) showed low understanding on the part of the Chinese public of GE technology, with only 11.9% of respondents having a positive view of GE food. With a history of food safety issues, the Chinese public may be more resistant to novel foodstuffs than other publics, but unfamiliarity with and suspicion of GE products characterize publics of many countries. More effective science and risk communication will be needed to promote public acceptance of IRGE crops and other products of agricultural biotechnology (31, 59).

Supplemental Material >

International Trade

The high level of international trade in commodity crops raises issues of GE content, given that IRGE crops are shipped to the wider world from countries where they are approved. For example, China, India, and Korea have rejected shipments of corn originating in the United States because they contained material from GE lines that these countries had not approved (68). Although the Bt63 rice line has not been commercialized in China, a small amount entered marketing channels, resulting in low-level presence of Bt63 content in food products shipped to Europe (**https://ec.europa.eu/food/safety/rasff_en**). Full realization of the ecological and socioeconomic benefits of IRGE crops is thus impacted by lack of harmonization among the biotechnology policies of trading nations (60).

OUTLOOK

Given recent economic development and a rising standard of living, promoting ecological sustainability has become a major issue for China. Agricultural biotechnology may provide an opportunity for a green revolution for China's agriculture. To accelerate commercialization of GE crops, based on the issues discussed above, China may need to (*a*) strengthen policy guidance and implement long-term programs for scientific and technological development, promoting innovation capacity in agro-biotechnological research and development; (*b*) promote confidence in development and application of GE crops, attracting business investment and fostering leading enterprises in this industry; (*c*) strengthen the development of the GE plant biosafety regulatory system and expedite GE crop regulatory process; and (*d*) develop and implement a well-targeted biotechnology public outreach program to counter negative messaging from anti-biotechnology groups. These measures are also likely to be appropriate for some other developing countries.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We are grateful to Dr. Qingsong Liu (Xinyang Normal University, China) for help in collection of the data on insect-resistant genetically engineered events developed in China, Dr. Liu Wei and Yan Yang (Institute of Plant Protection, CAAS) for assistance in making the illustrations, and Prof. Anthony M. Shelton (Cornell University, USA) for constructive comments on an early draft of this review. The present study was supported by the National GMO New Variety Breeding Program of the People's Republic of China (2016ZX08011-001).

LITERATURE CITED

1. Abbas HK, Zablotowicz RM, Weaver MA, Shier WT, Bruns HA, et al. 2013. Implications of Bt traits on mycotoxin contamination in maize: overview and recent experimental results in southern United States. *J. Agric. Food Chem.* 61:11759–70
2. Abedullah KS, Qaim M. 2005. *Bt* cotton, pesticide use and environmental efficiency in Pakistan. *J. Agric. Econ.* 66:66–86
3. Adamczyk JJ, Greenberg S, Armstrong JS, Mullins WJ, Braxton LB, et al. 2008. Evaluation of Bollgard®, Bollgard II®, and WideStrike® technologies against beet and fall armyworm larvae (Lepidoptera: Noctuidae). *Fla. Entomol.* 91:531–36

4. Adenle AA, Morris EJ, Murphy DJ, Phillips PWB, Trigo E, et al. 2018. Rationalizing governance of genetically modified products in developing countries. *Nat. Biotechnol.* 36(2):137–39
5. Bajwa U, Sandhu KS. 2014. Effect of handling and processing on pesticide residues in food: a review. *J. Food Sci. Technol.* 51:201–20
6. Boobis AR, Ossendorp BC, Banasiak U, Hamey PY, Sebestyen I, Moretto A. 2008. Cumulative risk assessment of pesticide residues in food. *Toxicol. Lett.* 180:137–50
7. Brookes G, Barfoot P. 2015. GM crops: global socio-economic and environmental impacts 1996–2014. *AgBioForm* 8:187–96
8. Brookes G, Barfoot P. 2017. *GM Crops: Global Socio-Economic and Environmental Impacts 1996–2015*. Dorchester, UK: PG Econ.
9. Brookes G, Barfoot P. 2018. Farm income and production impacts of using GM crop technology 1996–2016. *GM Crops Food* 9:59–89
10. Carpenter J. 2010. Peer-reviewed surveys indicate positive impact of commercialized GM crops. *Nat. Biotechnol.* 28:319–21
11. Carrière Y, Crowder DW, Tabashnik BE. 2010. Evolutionary ecology of insect adaptation to *Bt* crops. *Evol. Appl.* 3:561–73
12. Carrière Y, Fabrick JA, Tabashnik BE. 2016. Can pyramids and seed mixtures delay resistance to *Bt* crops? *Trends Biotechnol*. 34:291–302
13. CAST (Counc. Agric. Sci. Technol.). 2018. *Regulatory barriers to the development of innovative agricultural biotechnology by small businesses and universities*. Issue Pap. 59, CAST, Ames, IA
14. Catarino R, Ceddia G, Areal FJ, Park J. 2015. The impact of secondary pests on *Bacillus thuringiensis* (*Bt*) crops. *Plant Biotechnol. J.* 13:601–12
15. Chen L, Lee D, Song Z, Suh H, Lu B. 2004. Gene flow from cultivated rice (*Oryza sativa*) to its weedy and wild relatives. *Ann. Bot.* 93:67–73
16. Chen M, Shelton A, Ye GY. 2011. Insect-resistant genetically modified rice in China: from research to commercialization. *Annu. Rev. Entomol.* 56:81–101
17. Chen M, Ye G, Hu C, Tu J, Datta S. 2003. Effect of transgenic *Bt* rice on dispersal of planthoppers and leafhoppers as well as their egg parasitic wasps. *J. Zhejiang Univ. Agric. Life Sci.* 29:29–33
18. Chen R, Huang J, Qiao F. 2013. Farmers' knowledge on pest management and pesticide use in *Bt* cotton production in China. *China Econ. Rev.* 27:15–24
19. Chen X, Yang C, Jia H. 2014. Issues confronting GMO crops in China. *J. Huanzhong Agric. Univ.* 33:118–20
20. Chen Y, Tian J, Wang W, Fang Q, Akhtar ZR, et al. 2012. *Bt* rice expressing Cry1Ab does not stimulate an outbreak of its non-target herbivore, *Nilaparvata lugens*. *Transgenic Res.* 21:279–91
21. Cui K, Shoemaker SP. 2018. Public perception of genetically-modified (GM) food: a nationwide Chinese consumer study. *NPJ Sci. Food* 2:10
22. Dang C, Lu Z, Wang L, Chang X, Wang F, et al. 2017. Does *Bt* rice pose risks to non-target arthropods? Results of a meta-analysis in China. *Plant Biotechnol. J.* 15:1047–53
23. Dively GP, Venugopal PD, Bean D, Whalen J, Holmstrom K, et al. 2018. Regional pest suppression associated with widespread *Bt* maize adoption benefits vegetable growers. *PNAS* 115:3320–25
24. Dorhout DL, Rice ME. 2010. Intraguild competition and enhanced survival of western bean cutworm (Lepidoptera: Noctuidae) on transgenic Cry1Ab (MON810) *Bacillus thuringiensis* corn. *J. Econ. Entomol.* 103:54–62
25. Du D, Geng C, Zhang X, Zhang Z, Zheng Y, et al. 2013. Transgenic maize lines expressing a *cry1C** gene are resistant to insect pests. *Plant Mol. Biol. Rep.* 32:549–57
26. Duan JJ, Lundgren JG, Naranjo S, Marvier M. 2010. Exrapolating non-target risk of *Bt* crops from laboratory to field. *Biol. Lett.* 6:74–77
27. Duan JJ, Marvier M, Huesing J, Dively G, Huang ZY. 2008. A meta-analysis of effects of *Bt* crops on honey bees (Hymenoptera: Apidae). *PLOS ONE* 3(1):e1415
28. Ferré J, Van Rie J, MacIntosh SC. 2008. Insecticidal genetically modified crops and insect resistance management. In *Integration of Insect-Resistant Genetically Modified Crops Within IPM Programs*, ed. J Romeis, AM Shelton, GG Kennedy, pp. 41–86. Berlin: Springer

29. Folcher L, Delos M, Marengue E, Jarry M, Weissenberger A, et al. 2010. Lower mycotoxin levels in *Bt* maize grain. *Agron. Sustain. Dev.* 30:711–19
30. Gould F. 1998. Sustainability of transgenic insecticidal cultivars: integrating pest genetics and ecology. *Annu. Rev. Entomol.* 43:701–26
31. Han F, Shelton AM, Zhou D. 2016. How China can enhance adoption of biotech crops. *Nat. Biotechnol.* 34(7):693
32. Han L, Jiang X, Peng Y. 2016. Potential resistance management for the sustainable use of insect-resistant genetically modified corn and rice in China. *Curr. Opin. Insect Sci.* 15:139–43
33. Hellmich RL, Albajes R, Bergvinson D, Prasifka JR, Wang Z, et al. 2008. The present and future role of insect-resistant genetically modified maize in IPM. In *Integration of Insect-Resistant Genetically Modified Crops Within IPM Programs*, ed. J Romeis, AM Shelton, GG Kennedy, pp. 119–58. Berlin: Springer
34. Hirai K. 1995. Migration of the oriental armyworm *Mythimna separata* in East Asia in relation to weather and climate. III. Japan. In *Insect Migration Tracking Resources Through Space and Time*, ed. VA Drake, AG Gatehouse, pp. 117–30. Cambridge, UK: Cambridge Univ. Press
35. Hossain F, Pray CE, Lu Y, Huang J, Fan C, et al. 2004. Genetically modified cotton and farmers' health in China. *Int. J. Occup. Environ. Health* 10:296–303
36. Hu N, Hu J, Jiang X, Lu Z, Peng Y, et al. 2014. Establishment and optimization of a regionally applicable maize gene-flow model. *Transgenic Res.* 23:795–807
37. Huang F, Andow DA, Buschman LL. 2011. Success of the high-dose/refuge resistance management strategy after 15 years of *Bt* crop use in North America. *Entomol. Exp. Appl.* 141:1–16
38. Huang J, Hu R, Meijl HV, Tongeren FV. 2003. Economic impacts of genetically modified crops in China. *Genet. Mol. Biol.* 24:183–90
39. Huang J, Hu R, Qiao F, Yin Y, Liu H, et al. 2015. Impact of insect-resistant GM rice on pesticide use and farmers' health in China. *Sci. China Life Sci.* 58(5):466–71
40. Huang J, Hu R, Rozelle S, Pray C. 2005. Insect-resistant GM rice in farmers' fields: assessing productivity and health effects in China. *Science* 308:688–90
41. Huang J, Hu R, Rozelle S, Qiao F, Pray CE. 2002. Transgenic varieties and productivity of smallholder cotton farmers in China. *Austral. J. Agric. Resour. Econ.* 46:367–87
42. Huang J, Peng B. 2015. Consumers' perceptions on GM food safety in urban China. *J. Integr. Agric.* 14(11):2391–400
43. Huang Y, Wan P, Zhang H, Huang M, Li Z, et al. 2013. Diminishing returns from increased percent *Bt* cotton: the case of pink bollworm. *PLOS ONE* 8(7):e68573
44. Hutchison WD, Burkness EC, Mitchell PD, Moon RD, Leslie TW, et al. 2010. Areawide suppression of European corn borer with *Bt* maize reaps savings to non-*Bt* maize growers. *Science* 330:222–25
45. Icol I, Stotzky G. 2008. Fate and effects of insect-resistant *Bt* crops in soil ecosystems. *Soil Biol. Biochem.* 40:559–86
46. ISAAA (Int. Serv. Acquis. Agri-Biotech Appl.). 2017. *Global status of commercialized biotech/GM crops in 2017: Biotech crop adoption surges as economic benefits accumulate in 22 years*. ISAAA Brief 53, ISAAA, Ithaca, NY
47. Jia S, Yuan Q, Pei X, Wang F, Hu N, et al. 2014. Rice transgene flow: its patterns, model and risk management. *Plant Biotechnol. J.* 12:1259–70
48. Jiang S, Wu H, Liu H, Zheng J, Lin Y, Chen H. 2017. The overexpression of insect endogenous small RNAs in transgenic rice inhibits growth and delays pupation of striped stem borer (*Chilo suppressalis*). *Pest Manag. Sci.* 73:1453–61
49. Jiang Y, Li C, Zeng J, Liu J. 2014. Population dynamics of the armyworm in China: a review of the past 60 years' research. *Chinese J. Appl. Entomol.* 51(4):890–98
50. Jiao Y, Hu X, Peng Y, Wu K, Romeis J, et al. 2018. *Bt* rice plants may protect neighboring non-*Bt* rice plants against the striped stemborer *Chilo suppressalis. Proc. R. Soc. B* 285:20181283
51. Jin L, Zhang H, Lu Y, Yang Y, Wu K, et al. 2015. Large-scale test of the natural refuge strategy for delaying insect resistance to transgenic *Bt* crops. *Nat. Biotechnol.* 33:169–74
52. Kouser S, Qaim M. 2011. Impact of *Bt* cotton on pesticide poisoning in smallholder agriculture: a panel data analysis. *Ecol. Econ.* 70(11):2105–13

53. Lee JH, Uhm KB. 1995. Migration of the Oriental armyworm *Mythimna separata* in East Asia in relation to weather and climate. II. Korea. In *Insect Migration Tracking Resources Through Space and Time*, ed. VA Drake, AG Gatehouse, pp. 105–16. Cambridge, UK: Cambridge Univ. Press
54. Li B, Xu Y, Han C, Han L, Hou M, et al. 2015. *Chilo suppressalis* and *Sesamia inferens* display different susceptibility responses to Cry1A insecticidal proteins. *Pest Manag. Sci.* 71:1433–40
55. Li G, Ji T, Sun X, Jiang Y, Wu K, et al. 2019. Susceptibility evaluation of invaded *Spodoptera frugiperda* population in Yunnan province to five Bt proteins. *Plant Prot*. 45:15–20
56. Li N, He K, Cui L, Wang Z. 2011. Environmental safety of genetically modified insect resistant maize and future perspectives for implementation in China. *Plant Protect*. 37:18–26
57. Li R, He L, Wei W, Hao L, Ji X, et al. 2015. Chlorpyrifos residue levels on field crops (rice, maize and soybean) in China and their dietary risks to consumers. *Food Control* 51:212–17
58. Li Y, Gao Y, Wu K. 2017. Function and effectiveness of natural refuge in IRM strategies for *Bt* crops. *Curr. Opin. Insect Sci.* 21:1–6
59. Li Y, Hallerman EM, Liu Q, Wu K, Peng Y. 2016. The development and status of *Bt* rice in China. *Plant Biotechnol. J.* 14:839–48
60. Li Y, Hallerman EM, Peng Y. 2018. How can China prepare for the domestic cultivation of *Bt* maize? *Trends Food Sci. Technol.* 73:87–88
61. Li Y, Lu Y, Hallerman EM, Peng Y, Wu K. 2017. Commercial use and governance of *Bt* cotton in China. 2017. In *Genetically Modified Organisms in Developing Countries*, ed. AA Adenle, EJ Morris, DJ Murphy, pp. 225–35. Cambridge, UK: Cambridge Univ. Press
62. Li Y, Romeis J, Wu K, Peng Y. 2014. Tier-1 assays for assessing the toxicity of insecticidal proteins produced by genetically engineered plants to non-target arthropods. *Insect Sci*. 21:125–34
63. Li Y, Zhang Q, Liu Q, Meissle M, Yang Y, et al. 2017. *Bt* rice in China: focusing the non-target risk assessment. *Plant Biotechnol. J.* 15(10):1340–45
64. Lin K, Hou M, Han L, Liu Y. 2008. Research progress in host selection and underlying mechanisms, and factors affecting population dynamics of *Chilo suppressalis. Plant Protect*. 34(1):22–28
65. Liu L, Cao C. 2014. Who owns the intellectual property rights to Chinese genetically modified rice? Evidence from patent portfolio analysis. *Biotechnol. Law Rep.* 33(5):181–92
66. Liu QS, Hallerman E, Peng YF, Li YH. 2016. Development of *Bt* rice and *Bt* corn in China and their efficacy in target pest control. *Int. J. Mol. Sci.* 17(10):1561
67. Liu Z, Guo W, Zhu X, Zhu Z, Zhang T. 2003. Inheritance analysis of resistance of transgenic *Bt+GNA* cotton line to *Helicoverpa armigera*. *J. Agric. Biotechnol*. 11(4):388–93
68. Lopez R. 2013. China rejects shipment of genetically modified corn. *Los Angeles Times*, Dec 27. **https://www.latimes.com/business/la-fi-mo-china-rejects-shipment-of-gmo-corn-20131227-story.html**
69. Lu B. 2016. Challenges of transgenic crop commercialization in China. *Nat. Plants* 2(6):16077
70. Lu B, Snow AA. 2005. Gene flow from genetically modified rice and its environmental consequences. *Bioscience* 55:669–78
71. Lu Y. 2012. Advance in insect pest management in *Bt* cotton worldwide. *Chinese J. Appl. Entomol.* 49:809–19
72. Lu Y, Liang G. 2016. Research advance on the succession of insect pest complex in *Bt* crop ecosystem. *Plant Protect*. 42:7–11
73. Lu Y, Wu K. 2011. Mirid bugs in China: pest status and management strategies. *Outlooks Pest Manag*. 22:248–52
74. Lu Y, Wu K, Jiang Y, Guo Y, Desneux N. 2012. Widespread adoption of *Bt* cotton and insecticide decrease promotes biocontrol services. *Nature* 487:362–65
75. Lu Y, Wu K, Jiang Y, Xia B, Li P, et al. 2010. Mirid bug outbreaks in multiple crops correlated with wide-scale adoption of *Bt* cotton in China. *Science* 328:1151–54
76. Mao Y, Tao X, Xue X, Wang L, Chen X. 2011. Cotton plants expressing CYP6AE14 double-stranded RNA show enhanced resistance to bollworms. *Transgen. Res.* 20:665–73
77. Mao Y, Xue X, Tao X, Yang C, Wang L, et al. 2013. Cysteine protease enhances plant-mediated bollworm RNA interference. *Plant Mol. Biol.* 83:119–29

78. Marvier M, McCreedy C, Regetz J, Kareiva P. 2007. A meta-analysis of effects of *Bt* cotton and maize on nontarget invertebrates. *Science* 316:1475–77
79. Matten SR, Frederick RJ, Reynolds AH. 2012. United States Environmental Protection Agency insect resistance management programs for plant-incorporated protectants and use of simulation modeling. In *Regulation of Agricultural Biotechnology: The United States and Canada*, ed. CA Wozniak, A McHughen, pp. 175–267. Berlin: Springer
80. Meissle M, Romeis J, Bigler F. 2011. *Bt* maize and integrated pest management: a European perspective. *Pest Manag. Sci.* 67:1049–58
81. Michel AP, Krupke CH, Baute TS, Difonzo CD. 2010. Ecology and management of the western bean cutworm (Lepidoptera: Noctuidae) in corn and dry Beans. *J. Integr. Pest Manag.* 1:A1–10
82. Miller JD. 2008. Mycotoxins in small grains and maize: old problems, new challenges. *Food Addit. Contam. A* 25:219–30
83. Nag SK, Raikwar MK. 2011. Persistent organochlorine pesticide residues in animal feed. *Environ. Monit. Assess.* 174:327–35
84. Naranjo SE. 2011. Impacts of *Bt* transgenic cotton on integrated pest management. *J. Agric. Food Chem.* 59:5842–51
85. Naranjo SE, Ruberson JR, Sharma HC, Wilson L, Wu K. 2008. The present and future role of insect-resistant genetically modified cotton in IPM. In *Integration of Insect-Resistant Genetically Modified Crops Within IPM Programs*, ed. J Romeis, AM Shelton, GG Kennedy, pp. 119–58. Berlin: Springer
86. NASEM (Natl. Acad. Sci. Eng. Med.). 2016. *Genetically Engineered Crops: Experiences and Prospects*. Washington, DC: Natl. Acad. Press
87. Neher DA, Muthumbi AWN, Dively GP. 2014. Impact of coleopteran-active *Bt* corn on non-target nematode communities in soil and decomposing corn roots. *Soil Biol. Biochem.* 76:127–35
88. Ni M, Ma W, Wang X, Gao M, Dai Y, et al. 2017. Next-generation transgenic cotton: Pyramiding RNAi and *Bt* counters insect resistance. *Plant Biotechnol. J.* 15:1204–13
89. NRC (Natl. Res. Counc.). 2010. *The Impact of Genetically Engineered Crops on Farm Sustainability in the United States*. Washington, DC: Natl. Acad. Press
90. Pott A, Otto M, Schulz R. 2018. Impact of genetically modified organisms on aquatic environments: review of available data for the risk assessment. *Sci. Total Environ.* 635:687–98
91. Pray CE, Huang J, Hu R, Rozelle S. 2002. Five years of *Bt* cotton in China: the benefits continue. *Plant J.* 31:423–30
92. Qaim M. 2009. The economics of genetically modified crops. *Annu. Rev. Resour. Econ.* 1:665–93
93. Qi G, Lv L, Lan R, Xie J, Zhang W. 2011. Tracking the source regions of *Cnaphalocrocis medinalis* in the rice growing region of northern Guangdong Province. *Chinese J. Appl. Entomol.* 50(3):601–7
94. Qiao F. 2015. Fifteen years of *Bt* cotton in China: the impact and its dynamics. *World Dev*. 70:177–85
95. Qiao F, Huang J. 2019. Genetically modified (GM) rice versus non-GM rice: pesticide use and yield—a case study. *Sci. China Life Sci.* In press
96. Qiao F, Huang J, Wang X. 2017. Fifteen years of *Bt* cotton in China: results from household surveys. *World Dev*. 98:351–59
97. Qiao F, Huang J, Zhang C. 2016. The sustainability of the farm-level impact of *Bt* cotton in China. *J. Agric. Econ.* 67(3):602–18
98. Raybould A, Quemada H. 2010. *Bt* crops and food security in developing countries: realised benefits, sustainable use and lowering barriers to adoption. *Food Secur*. 2(3):247–59
99. Romeis J, Bartsch D, Bigler F, Candolfi MP, Gielkens MMC, et al. 2008. Assessment of risk of insect-resistant transgenic crops to nontarget arthropods. *Nat. Biotechnol.* 26:203–8
100. Romeis J, Meissle M, Bigler F. 2006. Transgenic crops expressing *Bacillus thuringiensis* toxins and biological control. *Nat. Biotechnol.* 24:63–71
101. Romeis J, Raybould A, Bigler F, Candolfi MP, Hellmich RL, et al. 2013. Deriving criteria to select arthropod species for laboratory tests to assess the ecological risks from cultivating arthropod-resistant genetically engineered crops. *Chemosphere* 90:901–9
102. Rong J, Lu B, Song Z, Su J, Snow A, et al. 2007. Dramatic reduction of crop-to-crop gene flow within a short distance from transgenic rice fields. *New Phytol*. 173:346–53

103. Rong J, Song Z, Su J, Xia H, Lu B, et al. 2005. Low frequency of transgene flow from *Bt/CpTI* rice to its nontransgenic counterparts planted at close spacing. *New Phytol*. 168:559–66
104. Rong J, Song Z, Su J, Xia H, Lu B, Wang F. 2006. Low frequencies of transgene flow between *Bt/CpTI* rice and their non-transgenic counterparts under alternating cultivation. *Biodiv. Sci.* 14:309–14
105. Shankar B, Thirtle C. 2005. Pesticide productivity and transgenic cotton technology: the South African smallholder case. *J. Agric. Econ.* 56:97–116
106. Shelton AM, Badenes-Perez FR. 2006. Concepts and applications of trap cropping in pest management. *Annu. Rev. Entomol.* 51:285–308
107. Sheng C, Wang H, Sheng S, Gao L, Xuan W. 2003. Pest status and loss assessment of crop damage caused by the rice borers, *Chilo suppressalis* and *Tryporyza incertulas* in China. *Chinese J. Appl. Entomol.* 40:289–94
108. Sobek EA, Munkvold GP. 1999. European corn borer (Lepidoptera: Pyralidae) larvae as vectors of *Fusarium moniliforme*, causing kernel rot and symptomless infection of maize kernels. *J. Econ. Entomol.* 92:503–9
109. Song L, Wei L, Wang Z, He K, Cong B. 2009. Effect of infestation by the Asian corn borer together with *Fusarium verticillioides* on corn yield loss. *Acta Phytophylacica Sin*. 36:487–90
110. Subramanian A, Qaim M. 2009. Village-wide effects of agricultural biotechnology: the case of *Bt* cotton in India. *World Dev*. 37:256–67
111. Sun H, Zhang F. 2014. Analysis on the GMO's intellectual property strategy in China. *Agric. Econ.* 2:11–16
112. Tabashnik BE, Brévault T, Carrière Y. 2013. Insect resistance to *Bt* crops: lessons from the first billion acres. *Nat. Biotechnol.* 31:510–21
113. Tabashnik BE, Gassmann AJ, Crowder DW, Carriére Y. 2008. Insect resistance to *Bt* crops: evidence versus theory. *Nat. Biotechnol.* 26:199–202
114. Wan P, Huang Y, Tabashnik BE, Huang M, Wu K. 2012. The halo effect: suppression of pink bollworm on non-*Bt* cotton by *Bt* cotton in China. *PLOS ONE* 7(7):e42004
115. Wan P, Wu K, Huang M, Wu J. 2004. Seasonal pattern of infestation by pink bollworm *Pectinophora gossypiella* (Saunders) in field plots of *Bt* transgenic cotton in the Yangtze River valley of China. *Crop Protect*. 23:463–67
116. Wan P, Wu K, Huang M, Yu D, Wu J. 2008. Population dynamics of *Spodoptera litura* (Lepidoptera: Noctuidae) on *Bt* cotton in the Yangtze River Valley of China. *Environ. Entomol.* 37:1043–48
117. Wan P, Xu D, Cong S, Jiang Y, Huang Y, et al. 2017. Hybridizing transgenic *Bt* cotton with non-*Bt* cotton counters resistance in pink bollworm. *PNAS* 114:5413–18
118. Wang F, Hu G, Chen X, Shen H, Luo S, et al. 2009. Analysis on the causes of recent outbreaks of *Cnaphalocrocis medinalis* in Nanning, China. *Chinese J. Rice Sci.* 23(5):537–45
119. Wang X, Liu Q, Meissle M, Peng Y, Wu K, et al. 2018. *Bt* rice could provide ecological resistance against nontarget planthoppers. *Plant Biotechnol. J.* 16:1748–55
120. Wei T, Zhu W, Pang M, Liu Y, Wang Z, et al. 2013. Influence of the damage of cotton bollworm and corn borer to ear rot in corn. *J. Maize Sci.* 21(4):116–18
121. Wolfenbarger LL, Naranjo SE, Lundgren JG, Bitzer RJ, Watrud LS. 2008. *Bt* crop effects on functional guilds of non-target arthropods: a meta-analysis. *PLOS ONE* 3(5):e2118
122. Wu K. 2007. Monitoring and management strategy for *Helicoverpa armigera* resistance to *Bt* cotton in China. *J. Invert. Pathol.* 95:220–23
123. Wu K, Feng H, Guo Y. 2004. Evaluation of maize as a refuge for management of resistance to *Bt* cotton by *Helicoverpa armigera* (Hubner) in the Yellow River cotton-farming region of China. *Crop Protect*. 23:523–30
124. Wu K, Guo Y. 2005. The evolution of cotton pest management practices in China. *Annu. Rev. Entomol.* 50:31–52
125. Wu K, Guo Y, Gao S. 2002. Evaluation of the natural refuge function for *Helicoverpa armigera* (Lepidoptera: Noctuidae) within *Bacillus thuringiensis* transgenic cotton growing areas in North China. *J. Econ. Entomol.* 95:832–37

126. Wu K, Lu Y, Feng H, Jiang Y, Zhao J. 2008. Suppression of cotton bollworm in multiple crops in China in areas with *Bt* toxin-containing cotton. *Science* 321:1676–78
127. Wu X, Yang C, Mao Y, Wang L, Shangguan X, et al. 2016. Targeting insect mitochondrial complex I for plant protection. *Plant Biotechnol. J.* 14:1925–35
128. Xia Z, Pan H, Zhang L, Liu C. 1995. The relationship between corn ear rot caused by *Fusarium moniliforme* and corn ear-feeding rate caused by Asian borer (*Ostrinia furnacalis*). *China Acad. J. Electron. Publ. House* 10:88–91
129. Xie W, Ali T, Cui Q, Huang J. 2017. Economic impacts of commercializing insect-resistant GM maize in China. *China Agric. Econ. Rev.* 9:340–54
130. Xu L, Wang Z, Zhang J, He K, Ferry N, et al. 2010. Cross-resistance of Cry1Ab-selected Asian corn borer to other Cry toxins. *J. Appl. Entomol.* 134:429–38
131. Yang F, Kerns D, Huang F. 2015. Refuge-in-the-bag strategy for managing insect resistance to *Bt* maize. *Outlooks Pest Manag*. 26(5):226–28
132. Yang J, Yang Y, Bao Y, Lu P. 2008. Effects of transgenic cotton varieties on nutrition development and α-NA carboxylesterase activity of *Prodenia litura* (Fabricius). *Jiangsu J. Agric. Sci.* 24:210–12
133. Yang Y, Zhang B, Zhou X, Romeis J, Peng Y, et al. 2018. Toxicological and biochemical analyses demonstrate the absence of lethal or sublethal effects of cry1C- or cry2A-expressing *Bt* rice on the collembolan *Folsomia candida*. *Front. Plant Sci*. 9:131
134. Yu X, Xu H, Lv Z, Chen J, Zheng X, Tao L. 2002. Differentiation of striped stem borer (SSB), *Chilo suppressalis* Walker from rice and *Zizania caduciflora* habitats. *Acta Ecol. Sin.* 22(3):341–45
135. Yuan Z, Wang W, Wang Z, He K, Bai S. 2015. Host plants of the Asian corn borer, *Ostrinia furnacalis* (Guenée) (Lepidoptera: Crambidae). *J. Plant Protect.* 42:957–64
136. Zhang F, Liu Y, Song J, Lei S, Ying Q, et al. 2012. Research on frequency of exogenous gene flow from marber-free insect-resistant transgenic rice to conventional rice varieties. *Agric. Sci. Technol.* 13:693–97
137. Zhang H, Tian W, Zhao J, Jin L, Yang J, et al. 2012. Diverse genetic basis of field-evolved resistance to *Bt* cotton in cotton bollworm from China. *PNAS* 109:10275–80
138. Zhang R, Wang Y, Meng Z, Sun G, Guo S. 2007. Retrospect and prospect of research on Chinese transgenic insecticidal cotton. *J. Agric. Sci. Technol.* 9:32–42
139. Zhang T, He M, Gatehouse AMR, Wang Z, Edwards M, et al. 2014. Inheritance patterns, dominance and cross-resistance of Cry1Ab- and Cry1Ac-selected *Ostrinia furnacalis. Toxins* 6:2694–707
140. Zhang W, Lu Y, van der Werf W, Huang J, Wu F, et al. 2018. Multidecadal, county-level analysis of the effects of land use, *Bt* cotton, and weather on cotton pests in China. *PNAS* 115:E7700–9
141. Zhang X, Chen P, Chen C, Yang Y. 2007. Effect of the transgenic *Bt* cotton on laboratory population increasing of the beet armyworm *Spodoptera exigua* Hübner. *Acta Phytophylacica Sin*. 34:391–95
142. Zhang X, Geng J, Zhou W. 1981. Research on the migration of rice leaf roller, *Cnaphalocrocis medinalis* Guenée in China. *J. Nanjing Agric. Coll.* 3:43–54
143. Zhao C, Jurat-Fuentes JL, Abdelgaffar HM, Pan H, Song F, et al. 2015. Identification of a new *cry1I*-type gene as a candidate for gene pyramiding in corn to control *Ostrinia* species larvae. *Appl. Environ. Microbiol.* 81:3699–705