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**Global Perspectives on Field-Evolved Resistance to Transgenic Bt Crops: A Special  
Collection**

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## Abstract

Crops genetically engineered to produce insect-killing proteins from *Bacillus thuringiensis* (Bt) have revolutionized management of some major pests, but their efficacy is reduced when pests evolve resistance. Practical resistance, which is field-evolved resistance that reduces the efficacy of Bt crops and has practical implications for pest management, has been reported in 26 cases in seven countries involving 11 pest species. This special collection includes six original papers that present a global perspective on field-evolved resistance to Bt crops. One is a synthetic review providing a comprehensive global summary of the status of the resistance or susceptibility to Bt crops of 24 pest species in 12 countries. Another evaluates the inheritance and fitness costs of resistance of *Diabrotica virgifera virgifera* to Gpp34/Tpp35Ab (formerly called Cry34/35Ab). Two papers describe and demonstrate advances in techniques for monitoring field-evolved resistance. One uses a modified F<sub>2</sub> screen for resistance to Cry1Ac and Cry2Ab in *Helicoverpa zea* in the United States. The other uses genomics to analyze nonrecessive resistance to Cry1Ac in *Helicoverpa armigera* in China. Two papers provide multi-year monitoring data for resistance to Bt corn in Spain and Canada, respectively. The monitoring data from Spain evaluate responses to Cry1Ab of the corn borers *Sesamia nonagrioides* and *Ostrinia nubilalis*, whereas the data from Canada track responses of *O. nubilalis* to Cry1Ab, Cry1Fa, Cry1A.105, and Cry2Ab. We hope the new methods, results, and conclusions reported here will spur additional research and help to enhance the sustainability of current and future transgenic insecticidal crops.

Key words: *Bacillus thuringiensis*, genetically engineered, sustainability, evolution, resistance management

Research on resistance to the insecticidal proteins of *Bacillus thuringiensis* (Bt) has exploded in the past few decades. Our search of the Scopus literature database found 4958 scientific publications on this topic including 1677 from 2016 to 2022 (240 per year) compared with only 167 from 1962 to 1989 (6 per year). Whereas the first review on evolution of resistance to Bt provided a comprehensive summary at the time (Tabashnik 1994), this is no longer feasible even with several articles. Accordingly, this special collection focuses on a key aspect of this rapidly growing area: field-evolved insect resistance to crops that have been genetically engineered to produce Bt proteins.

In the context of Bt crops, field-evolved (or field-selected) resistance is defined as a “genetically based decrease in susceptibility of an insect population to a Bt toxin caused by selection in the field” (Tabashnik and Carrière 2017). We emphasize the word “evolution” of resistance because this is an evolutionary phenomenon that entails changes in allele frequencies in populations. Recognizing this fact is essential for understanding and managing resistance. Moreover, resistance to Bt toxins and other pesticides provides some of the most compelling examples of evolution. Thus, we encourage use of the words “evolution” and “evolved” in reference to resistance rather than imprecise alternatives including “development” and “develop.”

This collection was inspired by a symposium on the same topic at the International Congress of Entomology in Helsinki, Finland in July 2022. We are grateful to Frank Zalom, one of the Congress organizers and Editor-in-Chief of the *Journal of Economic Entomology* (*JEE*), for inviting us to produce this special collection. We eagerly accepted his invitation in 2018. The pandemic delayed the conference as well as production of the papers for this special collection. The collection includes six papers published here for the first time that are led by scientists who

were invited to speak at the symposium, and ten related papers that were published in *JEE* from 1990 to 2018, including the first report of field-evolved resistance to Bt (Tabashnik et al. 1990).

## **Background**

Bt crops have revolutionized management of some major pests by suppressing them or even aiding in their eradication, thereby reducing conventional insecticide use and enhancing biological control (Hutchison et al. 2010, Dively et al. 2018, Romeis et al. 2019, Tabashnik et al. 2021). The Bt proteins produced by transgenic crops are highly effective against certain pests, yet not toxic to most nontarget organisms including people, other vertebrates, and arthropod natural enemies (Mendelsohn et al. 2003, Bravo et al. 2011, Comas et al. 2014, NASEM 2016, Meissle et al. 2022). Collectively, the hundreds of known Bt toxins can kill a wide variety of insects, but each toxin has a relatively narrow spectrum of activity (van Frankenhuyzen 2013).

The first Bt crops, Bt corn and cotton, were introduced commercially in 1996 with each producing a single Bt crystalline toxin (Cry1Ab and Cry1Ac, respectively) effective against only certain lepidopteran pests (Tabashnik et al. 2009). The spectrum of pests targeted by Bt crops expanded in 2003 with the introduction in the United States of Bt corn producing Cry3Bb, which kills rootworm beetles in the genus *Diabrotica* (Andow et al. 2016). Recently introduced Bt crops targeting lepidopterans include soybean and sugarcane in Brazil, eggplant in Bangladesh, and cowpea in Ghana and Nigeria (ISAAA 2019, Addae et al. 2020, Shelton et al. 2020, USDA FAS 2022). Cotton producing Cry51Aa (renamed Mpp51 by Crickmore et al. 2021) targeting hemipteran pests (Akbar et al. 2018) has been approved for cultivation in the United States (ISAAA GM Approval Database 2021).

In 2019, millions of farmers in 27 countries on six continents planted 109 million hectares (269 million acres) of Bt crops (Table 1, Figs. 1 and 2, ISAAA 2019). Some recent major plantings include 94% of the cotton in India in 2019 (12 million hectares of Bt cotton, ISAAA 2019), >73% of the soybean in Brazil in 2021-2022 (>30 million hectares of Bt soybean, Godoy et al. 2022), and 84% of the corn in the U.S. in 2022 (30 million hectares of Bt corn, USDA ERS 2022, USDA NASS 2023). Many widely cultivated Bt plants each produce more than one Bt toxin to broaden the spectrum of pests targeted, kill single pests with two or more unrelated toxins to delay evolution of resistance, or both (Carrière et al. 2016).

The cumulative total area of Bt crops planted globally from 1996 to 2019 was 1.1 billion hectares. Bt crop hectares worldwide more than doubled from 2009 (50 million hectares) to 2019, with a mean yearly increase of 5.8 million hectares for that decade. We are not aware of published data on global Bt crop hectares for 2020 to 2022. Under the conservative assumption that the annual area planted was the same in these three years as in 2019, an estimated 1.5 billion hectares (3.6 billion acres) of Bt crops was planted from 1996 to 2022. This massive long-term exposure to Bt crops has selected intensely for resistance to Bt toxins in some target pests.

### **Topics in the Collection**

Tabashnik et al. (2023 of this collection) summarize global resistance monitoring data from the first 25 years of Bt crops for 24 pest species (22 moths and 2 beetles) from 12 countries on six continents. Each case includes the resistance or susceptibility of one pest species in one country to one Bt toxin produced by one or more Bt crops (Bt corn, cotton, soybean, or sugarcane). The 73 cases cited consist of 26 cases of practical resistance (36%), 17 cases of early warning of resistance (23%), and 30 cases of no decrease in susceptibility (41%).

Practical resistance is defined as field-evolved resistance in which more than half of the individuals in a population are resistant and the field efficacy of the Bt crop has decreased (Tabashnik et al. 2014). Early warning of resistance entails field-evolved resistance that does not meet the additional criteria for practical resistance. Early warning of resistance does not necessarily mean that practical resistance is imminent. For example, data for responses of *Helicoverpa punctigera* to Cry2Ab in Australia during 2009 (Downes et al. 2010) and *Helicoverpa armigera* to Cry1Ac in China during 2010 (Zhang et al. 2011) fit the criteria for early warning, but neither case has progressed to practical resistance yet. No decrease in susceptibility indicates the monitoring data show no statistically significant decrease in susceptibility in any population tested after field populations have been exposed to a Bt crop (Tabashnik et al. 2014).

Tabashnik et al. (2023 of this collection) report that half of the 26 cases of practical resistance occur in three pests: *Helicoverpa zea* (5 cases), *Spodoptera frugiperda* (4 cases), and *Diabrotica virgifera virgifera* (4 cases). Also, four countries that planted 87% of the world's hectares of Bt crops in 2019 (Table 1) also account for 85% of the cases of practical resistance: the U.S. (13 cases), Brazil (4 cases), Argentina (3 cases), and India (2 cases). Overall, the global patterns of field-evolved resistance to Bt crops are consistent with the evolutionary principles underlying the refuge strategy. These principles and the empirical data support the idea that the following factors can delay evolution of resistance: abundant refuges of non-Bt host plants, recessive inheritance of resistance, low resistance allele frequency, fitness costs, incomplete resistance, and redundant killing by multi-toxin Bt crops.

Smith et al. (2023 of this collection) selected a strain of *D. v. virgifera* in the lab for resistance to Gpp34/Tpp35Ab1 (previously called Cry34/35Ab) and assessed two of the factors listed above: inheritance of resistance and fitness costs. On seedling mats of corn producing

Gpp34/Tpp35Ab1, survival was 67% for the resistant strain versus 0% for its unselected parent strain. The resistance was not recessive, with a value of 0.36 for  $h$ , which is intermediate between 0 indicating completely recessive resistance and 1 indicating completely dominant resistance. Relative to recessive inheritance, the observed nonrecessive inheritance could accelerate evolution of resistance. When reared on seedling mats of non-Bt corn, the resistant strain had slower development and lower egg viability than the unselected strain, which are fitness costs that would select against resistance in refuges.

Two papers in this collection describe and demonstrate advances in techniques for monitoring field-evolved resistance to Bt crops. Both papers analyze resistance in *Helicoverpa*. One focuses on *H. zea* in the United States, the other on the sibling species *H. armigera* in China. Santiago-González et al. (2023 of this collection) developed and implemented a modified F<sub>2</sub> screen for estimating the frequency of alleles conferring resistance. In a classic *JEE* paper, Andow and Alstad (1998) modified the standard F<sub>2</sub> screen from *Drosophila* genetics (e.g., Mackay and Bewley 1989) to estimate the frequency of rare recessive resistance alleles and to isolate resistant strains. In turn, Santiago-González et al. (2023 of this collection) modified the F<sub>2</sub> screen of Andow and Alstad (1998) by using crosses between three laboratory susceptible females and one wild male moth of *Helicoverpa zea* to establish F<sub>1</sub> family lines in the lab. This innovation overcomes limitations for *H. zea* associated with single-pair crosses, mass mating, or light trap collections (Santiago-González et al. 2023 of this collection). They report the frequency of resistance alleles was 0.72 for Cry1Ac and 0.22 for Cry2Ab based on 192 families established in 2019 to 2020 from ten field sites Arkansas, Louisiana, Mississippi, and Tennessee.

Guan et al. (2023 this collection) report one of the first studies using genomics to evaluate the genetic basis of resistance to Bt toxins in field populations. They developed and applied a

variant of a genomics mapping method called quantitative trait locus (QTL)-seq. They used this approach to analyze nonrecessive resistance to Cry1Ac in 21 backcross families derived in 2018 from eight field populations of *Helicoverpa armigera* in northern China. This analysis identified a region on chromosome 10 associated with nonrecessive resistance to Cry1Ac in all 21 of these families. Individual sequencing revealed that all 21 field-collected resistant grandparents of the backcross families had a previously identified dominant point mutation in the tetraspanin gene *HaTSPAN1* that occurs in the region of chromosome 10 identified by QTL-seq.

Two papers in this collection provide detailed summaries of multi-year monitoring of pest resistance to Bt corn in Spain and Canada, respectively. Each of these papers offers important new findings as well as broader insights when considered together and in light of previous work. Garcia et al. (2023 of this collection) report that after 23 years (1998 to 2021) of exposure to single-toxin Bt corn producing Cry1Ab in Spain, no decrease in susceptibility was detected in either of the two main target pests, the corn borers *Sesamia nonagrioides* and *Ostrinia nubilalis*. Whereas Bt corn producing more than one lepidopteran-active Bt protein is prevalent in the U.S. and other countries where Bt corn is cultivated extensively, growers in Europe have been limited to single-toxin Bt corn producing Cry1Ab. In Spain, the sustained susceptibility to Cry1Ab despite this constraint might have been facilitated by non-Bt corn consistently accounting for a relatively high percentage of all corn planted. During 2021, the percentage of corn hectares in Spain consisting of non-Bt corn was >75% nationally and at least 36% regionally (Garcia et al. 2023 of this collection).

The extremely low frequency of *O. nubilalis* alleles conferring resistance to Cry1Ab corn when this transgenic crop was first commercialized and soon after has probably also delayed evolution of resistance in Europe as well as in the U.S. No alleles conferring resistance to Cry1Ab corn were detected in F<sub>2</sub> screens of this pest conducted from 1999 to 2005 in 2156 lines from



Europe (France, Italy, Germany, and Slovakia) and from 1996 to 2003 in 933 lines from the U.S., which together represent 12,356 alleles screened (Andow et al. 1998, 2000; Bourguet et al. 2003, Stodola et al. 2006, Engels et al. 2010). These results indicate the Cry1Ab resistance allele frequency in *O. nubilalis* was well below 0.001. Moreover, several selection experiments with *O. nubilalis* failed to yield strains that could complete development on Cry1Ab corn (Alves et al. 2006, Siegfried and Hellmich 2012). Also, selection with Cry1Ab of a strain of *O. nubilalis* derived from greenhouses in Spain that had been repeatedly sprayed with Bt formulations containing Cry1Ab and other Bt proteins did not yield strong resistance to Cry1Ab (Crava et al. 2014).

In contrast with over two decades of sustained susceptibility of *O. nubilalis* to Cry1Ab in the U.S. and Europe, Smith et al. (2019) discovered practical resistance to Cry1Fa corn in Nova Scotia, Canada in 2018, 12 years after it was introduced there. Smith and Farhan (2023 of this collection) monitored responses of *O. nubilalis* in Canada from 2018 to 2020 to four toxins produced by Bt corn: Cry1Fa, Cry1Ab, Cry1A.105, and Cry2Ab. They report practical resistance to Cry1Fa at additional sites in Nova Scotia as well as in Quebec and Manitoba in 2019 and 2020, respectively. Their bioassays of 20 to 22 field-derived strains per toxin indicate no practical resistance to Cry1Ab, Cry1A.105, or Cry2Ab. However, for these three toxins, the small but statistically significant decreases in susceptibility detected in two to nine of the field-derived strains constitute early warnings of resistance.

We think one of the reasons *O. nubilalis* evolved practical resistance to Cry1Fa in corn in Canada but not the United States (Tabashnik et al. 2023 of this collection) is the higher exposure to this toxin in Canada. According to Smith et al. (2019), single-toxin Bt corn producing Cry1Fa was planted extensively in Nova Scotia from 2006 to 2018. By contrast, Siegfried et al. (2014) wrote that in Iowa and Nebraska of the US corn belt, it was unlikely that corn producing Cry1Fa

exceeded 20% of all corn before 2007. They also indicate that starting in 2009, single-toxin Cry1Fa corn was replaced by corn with more than one toxin targeting *O. nubilalis*.

Unlike the results with Cry1Ab noted above, lab selection with Cry1Fa produced strains of *O. nubilalis* that survived on Cry1Fa corn (Siegfried et al. 2014). Also, based on F<sub>2</sub> screens, the mean frequency of alleles conferring resistance to Cry1Fa corn in populations sampled from Iowa and Nebraska in 2008 and 2009 was 0.01 (Siegfried et al. 2014). A lab-selected strain with >3000-fold resistance to Cry1Fa was not cross-resistant to Cry1Ab (Pereira et al. 2008). The resistance to Cry1Fa in this strain was linked with the gene encoding the protein ABCC2, whereas resistance to Cry1Ab in another strain was not (Coates et al. 2013, Coates and Siegfried 2015). In *Ostrinia furnacalis*, CRISPR-mediated knockout of the *ABCC2* gene caused >300-fold resistance to Cry1Fa and only 3.6-fold resistance to Cry1Ab (Wang et al. 2020).

The enduring efficacy of Cry1Ab against *O. nubilalis* is one of the great success stories of Bt crops, particularly because this pest was predicted to evolve resistance to Bt corn in the U.S. in as little as three years under a worst-case scenario (Gould et al. 1997). Instead, this pest has remained susceptible for more than two decades and is now at historically low abundance in some parts of the U.S. corn belt (Tabashnik et al. 2023 of this collection). We think the past quarter century of Bt crops is just the beginning of the era of managing insect pests with transgenic crops. We hope the descriptions in this special collection of technical advances as well as lessons learned from successes and failures will help to sustain the next generations of transgenic crops for pest control.

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**Table 1.** Bt crop adoption by country in 2019.

Country <sup>a</sup>	Bt corn (M ha) <sup>b</sup>	Bt corn (%) <sup>c</sup>	Bt cotton (M ha) <sup>b</sup>	Bt cotton (%) <sup>c</sup>	All Bt crops (M ha) <sup>d</sup>
Brazil <sup>e</sup>	15.7	97	1.2	79	38.7
USA	29.9	83	5.0	94	34.9
India	0.0	0	11.9	94	11.9
Argentina	5.4	90	0.5	100	9.9
China	0.0	0	3.2	95	3.2
Pakistan	0.0	0	2.5	95	2.5
S. Africa	1.7	74	0.4	95	2.1
Paraguay	0.5	69	0.02	100	2.0
Canada	1.4	90	0.0	0	1.4
Philippines	0.9	61	0.0	0	0.9
Uruguay	0.1	82	0.0	0	0.5
Myanmar	0.0	0	0.3	86	0.3
Sudan	0.0	0	0.2	98	0.2
Mexico	0.0	0	0.2	93	0.2
Spain	0.1	22	0.0	0	0.1
Vietnam	0.1	10	0.0	0	0.1
Colombia	0.1	21	0.0	67	0.1
Australia <sup>f</sup>	0.0	0	0.1	98	0.1

<sup>a</sup> Based on data we compiled from ISAAA (2019). In 2019, the 18 countries listed above each planted more than 0.05 M ha (>50,000 ha) of Bt crops and collectively accounted for more than 99.9% of global Bt crop ha. Nine additional countries planted Bt crops on less than 0.05 M ha in 2019: Bt corn in Chile, Honduras, and Portugal; Bt cotton in Costa Rica, Eswatini, Ethiopia, Malawi, and Nigeria; and Bt eggplant in Bangladesh.

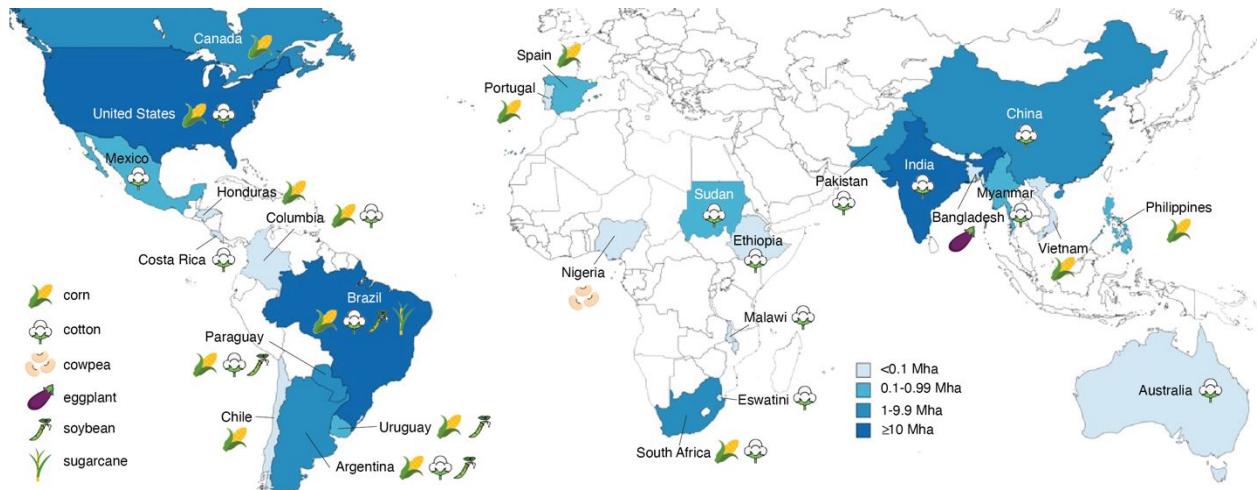
<sup>b</sup> Millions of hectares planted in 2019.

<sup>c</sup> Adoption (%) = 100% times Bt crop ha planted divided by total ha of the crop.

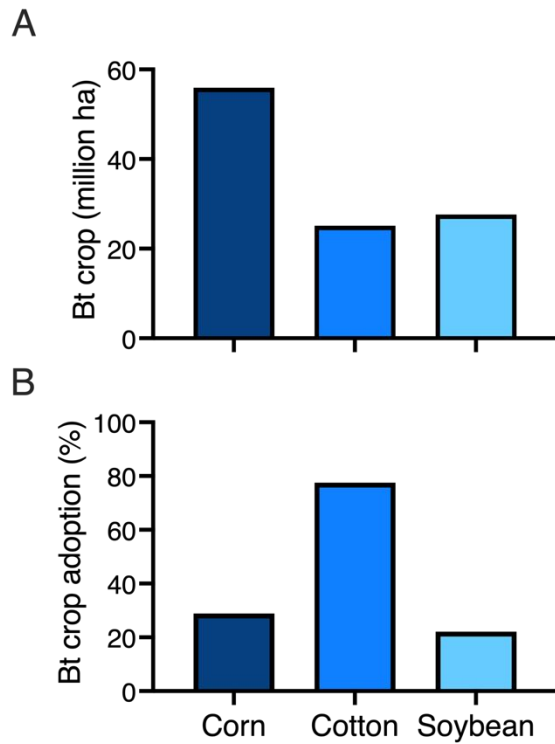
<sup>d</sup> Includes Bt corn, cotton, and soybean. Bt soybean was planted in the following four countries in 2019 (M ha, adoption): Brazil (21.7, 59%), Argentina (4.0, 23%), Paraguay (1.5, 43%), and Uruguay (0.4, 32%). These three crops accounted for >99.9% of Bt crop ha in 2019.

<sup>e</sup> In addition to Bt corn, cotton, and soybean, Brazil planted 0.018 M ha of Bt sugarcane in 2019.

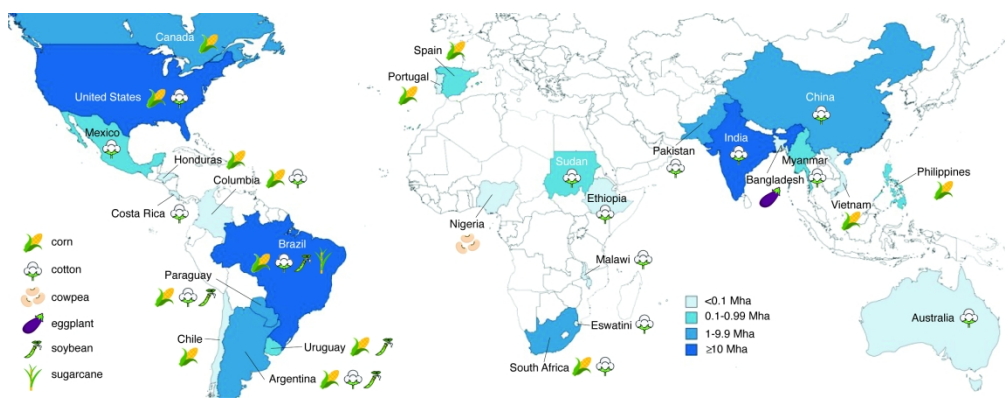
<sup>f</sup> Australia had 0.29 M ha of Bt cotton in 2018 and its total of 0.06 M ha in 2019 was unusually low because of drought.



**Fig. 1.** Six Bt crops planted in 27 countries in 2019. Data from ISAAA (2019).

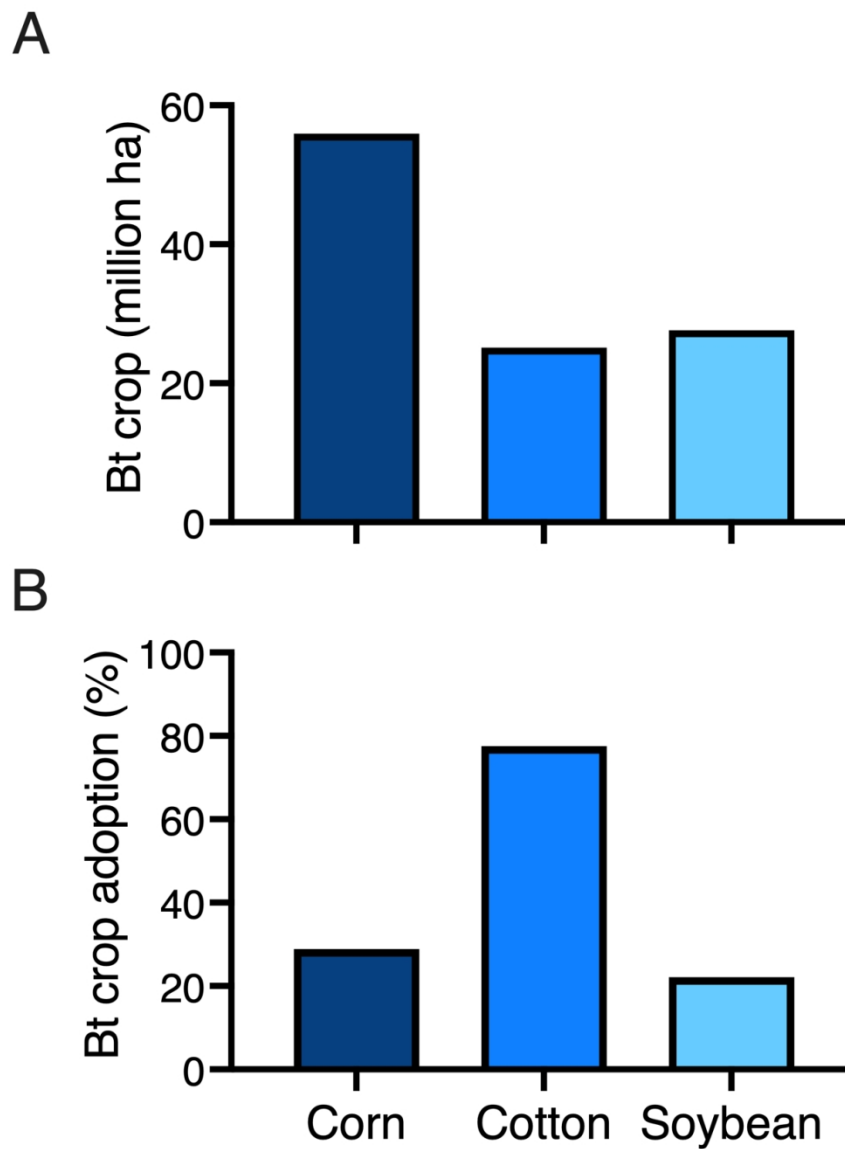


**Fig. 2.** Global planting of Bt corn, cotton, and soybean in 2019. A) Millions of hectares (ha) planted of each Bt crop. B) Bt crop adoption (%), which is 100% times the ha of Bt plants divided by the total ha of the same crop. Data on Bt crop ha from ISAAA (2019).



**Fig. 1.** Six Bt crops planted in 27 countries in 2019. Data from ISAAA (2019).

255x98mm (300 x 300 DPI)



**Fig. 2.** Global planting of Bt corn, cotton, and soybean in 2019. A) Millions of hectares (ha) planted of each Bt crop. B) Bt crop adoption (%), which is 100% times the ha of Bt plants divided by the total ha of the same crop. Data on Bt crop ha from ISAAA (2019).

122x145mm (300 x 300 DPI)