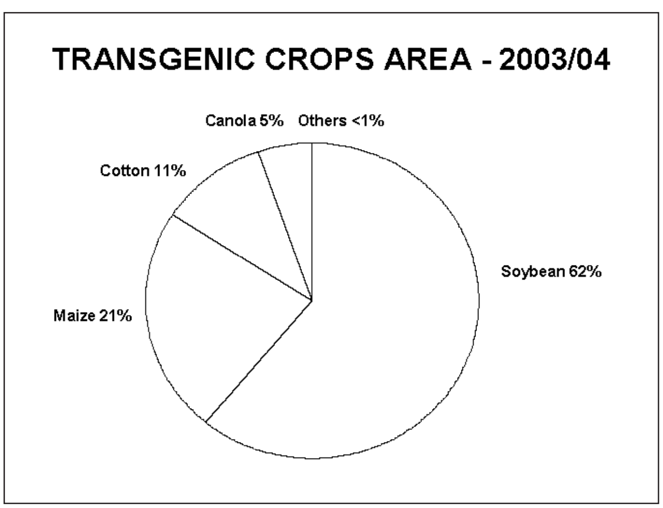
Update on Genetically Engineered Cotton

Genetic engineering technology is spreading, and more countries are adopting genetically engineered (GE) cotton varieties. Nine countries have commercialized GE cotton, and a few more are experimenting with the technology. However, a lack of national biosafety regulations and the cost of the technology are slowing adoption. Genetic engineering, as an additional tool for breeders to develop new varieties, has tremendous applications. The technology allows breeders to insert a specific gene or genes for specific traits. With conventional breeding, it is not possible to transfer only one gene at a time. Genes are linked, and in some cases, the linkage is very strong. So, if the desirable gene is close to a gene controlling an undesirable character, it is often not possible to break such a linkage and transfer only the desirable character. Moreover, conventional breeding is a long-term process, and genes can be moved within species or among species but not across genera. Some times even interspecies crosses are not possible. On the other hand, new characters can be acquired through transfer of non-cotton and non-related genes into cotton through genetic engineering.

The first transgenic cotton with a Bt gene, extracted from the soil bacterium *Bacillus thuringiensis*, expressing the protein at an economically viable level was developed in 1989. Bt cotton was commercially planted for the first time in 1996/97 in Australia and USA. According to the International Service for Acquisition of Agri-Biotech Applications (ISAAA), all transgenic crops were planted on 67.7 million hectares in 2003/04. A number of crops have been transformed, but soybean, maize, cotton and canola occupied about 99% of total GE area in 2003/04. Other crops that have been transformed include squash, tomato, papaya and others that were planted on less than 1% of the transgenic area in the world. Soybeans account for 61% of total area, followed by maize on 23% and cotton on 11%. Efforts have been made to improve a number of traits in various crops. But, insecticide and herbicide resistance are still the only two traits used on a commercial scale, apart from virus resistance and others planted on less than 1% of the total transgenic area.

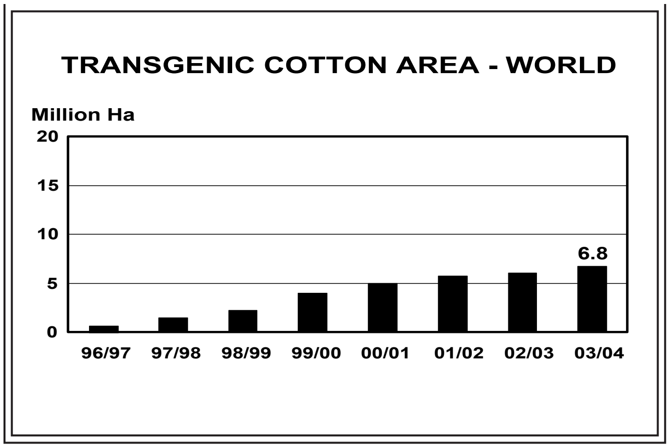


GE Cotton Area in the World

Transgenic cotton was planted on 6.8 million hectares in 2003/04, accounting for 21% of world cotton area and responsible for almost 30% production and 34% international trade. In December 2002, Monsanto received full U.S. regulatory clearance for its Bollgard II insect-protected cotton technology for large-scale use of a second Bt gene. 2003/04 was the first year that the proteins Cry2Ab and Cry1Ac were available in the form of Bollgard II for protection against bollworms. The purpose of Bollgard II is to have a dual gene resistance mechanism. The technology fee in the USA for Bollgard II is $99/ha, as against $79/ha for Bollgard only. Bollgard varieties will continue to be available, but plans are to replace them with Bollgard II varieties.

The US Department of Agriculture (USDA) and the Food and Drug Administration (FDA) have already confirmed the food, feed and environmental safety of Bollgard II. The Bollgard II technology has used the same soil bacterium as in the case of Bollgard, but it has two genes working at the same time. The primary objective remains the same, which is to control target insects that damage cotton bolls. However, the Bollgard II technology has some additional advantages over the Bollgard technology, some of which are long lasting and some are short-term.

- The basic objective of finding the 2nd Bt gene is to delay the development of resistance to the Bt toxin. Insects can develop resistance to one gene faster than to two genes working in the same genotype.
- The Cry1Ac in Bollgard causes much damage to tobacco budworm (*Heliothis virescens)*, and the American bollworm (*Helicoverpa armigera)* but it provides comparatively less resistance to other worms. The 2nd most important objective of inserting the 2nd gene was to extend the spectrum of bollworms and budworms controlled by Cry proteins. The Cry2Ab gene in Bollgard II provides equally good control of fall armyworm (*Spodoptera frugiperda)*, beet armyworm (*Spodoptera exigua)*, cabbage looper (*Trichoplusia ni)*, and soybean looper (*Pseudoplusia includens)* in addition to bollworms and budworms already controlled by Bollgard. The latest information from West Africa shows that Bollgard II has performed quite well against the red bollworm (*Diparopsis watersi)* in Burkina Faso in 2003/04.
- Some bollworms and budworms survive on Bollgard varieties, particularly towards the end of the fruit formation stage. The phenomenon, which occurs due to a smaller



amount of toxin in flowering parts, brings some loss in yield. The Cry1Ac levels are usually expressed 1 to 3 parts per million, while Cry2Ab is expressed from 7 to 19 parts per million. The higher dose of toxin in the plant in the form of Bollgard II technology will save the plant from late-season losses.

Cry1Ac (in Bollgard or Bt cotton elsewhere and Ingard in Australia) and Cry2Ab (in Bollgard II along with Cry1Ac) are protein toxins and can interact with each other and affect the performance of one or both toxins. However, studies have proved that there is no interaction between the two Cry proteins. Three isogenic lines of a variety having Cry1Ac only, Cry2Ab only and Cry1Ac+Cry2Ab were used to examine the relative contribution of each toxin to the total efficacy of Bollgard II, in addition to studying the nature of the interaction between the individual toxins in the 2-gene cotton. No interaction was proved. In 2003/04, Bollgard II was planted on a commercial scale in Australia and USA, and no negative results have been reported.

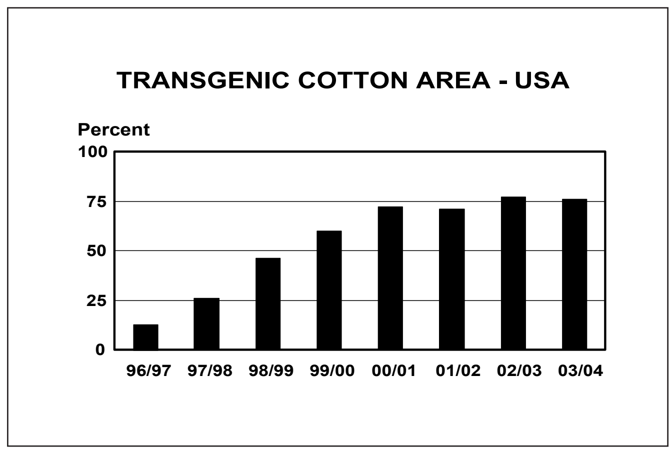
Area under Transgenic Cotton in Various Countries

GE cotton is commercially planted in Argentina, Australia, China (Mainland), Colombia, India, Indonesia, Mexico, South Africa and the USA. Indonesia planted only a few thousand hectares for the 2nd year in 2002/03 and there is no increase in area in 2003/04. In India, the Bt gene (Cry1Ac-Bollgard) has been introduced only through commercial cotton hybrids, and the three Bt hybrids were planted on 101,174 hectares in 2003/04. More hybrids have been approved in India for planting in 2004/05. Herbicide-resistant transgenic varieties are permitted for commercial cultivation in Argentina, Australia, South Africa and the USA. In other countries, only Bt cotton has been approved for commercial production. Estimated transgenic area in nine countries is as follows:

Transgenic Cotton Area 2003/04

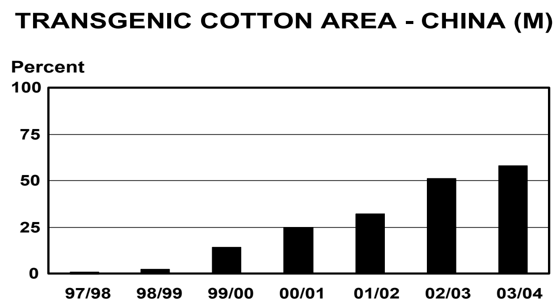
Country	Percent Area
Argentina	5-7%
Australia	30%
China (Mainland)	58%
India	1%
Indonesia	< 1%
Mexico	62%
South Africa	70-75%
USA	77%

GE cotton was planted on 77% of the total cotton area in the USA in 2003/04, and GE cotton occupied more than 70% of cotton area in the USA during the last five years. It seems that GE cotton has reached its peak in the USA, and increases should not be expected in 2004/05. Bollgard II was planted on small area but in the next few years most Bollgard will be replaced with Bollgard II varieties. Herbicide tolerance is the most popular character in cotton in the USA. Over four million hectares were planted to transgenic cotton varieties in the USA in 2003/04. Of the total GE cotton area in 2003/04, 37% area was planted to herbicide resistant varieties, 61% to stacked gene herbicide and insect resistant varieties, and only 2% was planted to insect resistant Bollgard or Bollgard II varieties.



GE cotton continues to gain popularity among farmers in China (Mainland), and insect resistant transgenic cotton area increased to 58% in 2003/04 from 51% last season. If the Yellow River Valley had not been hit by insect resistance to insecticides in the early 1990s, transgenic cotton may not be as popular today. China (Mainland) continues to expand insect resistant GE cotton developed domestically. It is estimated that 46% of the total GE cotton area in China (Mainland) in 2003/04 was from Monsanto and 54% was planted to a Bt cotton developed in China. No detailed and comparable data are available on the two genes. However, the popularity of the local gene indicates that it is equally effective against bollworms, particularly *Helicoverpa armigera*, which is the main pest in the Yellow River Valley and the Yangtze River Valley. The Xinjiang region does not grow GE cotton.

In India, Bt cotton is approved for use only in those states where commercial cotton hybrids are approved, and that does not include the North. Yields are higher in the North due to irrigation and better management practices, but hybrids have not been grown on a significant amount of area. Farmers in Haryana,



Rajasthan and Punjab states that form the North cotton zone are impressed from the performance last year of Bt hybrids in other regions, and they are anxious to grow Bt hybrids. Last year Mahyco-Monsanto had applied to the Genetic Engineering Approval Committee for approval of a Bt hybrid in the north of India but their request was rejected on the ground that the hybrid was susceptible to the leaf curl virus disease. This year, Rasi Seeds has received approval from the Genetic Engineering Approval Committee for large-scale trials of a Bt hybrid (RCH 2) in 2004/05. Although some farmers in the North may be experimenting with Bt hybrids on their own, Bt hybrids could be officially approved for commercial adoption in 2005/06. RCH 2 has been approved for cultivation in Madhya Pradesh, Chhattisgarh, Andhra Pradesh, Karnataka and Tamil Nadu. It was expected that 300,000 packets of 450 grams each will be sold in 2004/05. In India, the price of each packet of Bt hybrid seed is US$35.5, compared to the price of US$10 per packet in case of non-Bt hybrid seed. The packet includes seed for the refuge crop and, is enough to plant half a hectare.

New Technologies

Since the initiation of Bt cotton in commercial use in 1996/97, Bollgard II was the first new product to be approved as a replacement for Bollgard cotton. Three other products have been extensively researched for commercial release in the last few years, but only one has been approved so far. LibertyLink® cotton from Bayer CropScience was approved for commercial use. Three other products are close to approval, two insect resistant and one herbicide resistant. A lot of work is going on to improve many other features of cotton, including salt tolerance, stress tolerance and improved fiber quality, but no field tests have been reported on any of these products, indicating that they are years away from adoption.

LibertyLink® Cotton

LibertyLink® was approved for commercial adoption on March 10, 2004. The LibertyLink® herbicide's active ingredient is glufosinate-ammonium, commonly known as Ignite. Glufosinate-ammonium inhibits the enzyme glutamine synthetase in plants, leading to a rapid disruption of photosynthesis. LibertyLink® cotton will survive when Ignite is sprayed over the top of the crop. Ignite has low toxicity and is highly biodegradable. Ignite can be used to control grass weeds and broadleaf including troublesome weeds, such as morning glory, pigweed and Johnson grass. LibertyLink® cotton has a longer application window, up to the 10th leaf, and doses can be adjusted depending on the size of weeds, not the growth stage of the cotton. LibertyLink® cotton has been approved in the USA for use in most cotton growing states in 2004/05. LibertyLink® cotton will be available in FiberMax varieties. LibertyLink® cotton is not available with Bollgard or Bollgard II genes yet, but plans there are to produce stacked gene varieties in the future. LibertyLink canola and LibertyLink corn have been available commercially for several years.

Vegetative Insecticidal Protein (VIP) Cotton

VIP cotton is an alternate to Bollgard or Bollgard II that has been developed by Syngenta to control insects. The difference is that VIP cotton contains a vegetative insecticidal protein that controls target insects through a novel mode of action. Bollgard and Bollgard II utilize proteins from the *Bacillus thuringiensis* bacterium known as d-endotoxins. Bt d-endotoxins were discovered in the early 1900s, and have been used in many insect control applications other than cotton. The VIP protein is an exotoxin derived from the same soil bacterium *Bacillus thuringiensis*. As an exotoxin, the VIP protein is structurally, functionally and biochemically different than Bt d-endotoxins. The VIP protein is expressed in the entire cotton plant, including the floral parts, to provide protection against target species. When pest larvae feed on VIP cotton, the protein is ingested and causes the larvae to stop feeding and die. VIP is not approved for commercial use yet.

Wide Strike Cotton

WideStrike™ cotton from Dow AgroSciences is a combination of the Cry1Ac and Cry1F *Bacillus thuringiensis* proteins. Dow AgroSciences has field tested WideStrike™ for several years and is expecting approval from the government for planting in 2005/06. WideStrike™ delivers season-long protection against a broad spectrum of lepidopteran pests such as cotton bollworm, tobacco budworm, pink bollworm, beet armyworm, fall armyworm, southern armyworm, cabbage loopers and soybean loopers. WideStrike™ cotton was also tested in Australia in 2003/04.

VIP cotton and WideStrike™ have completed experimental stages and are awaiting government approval for commercial use. It is not known if the approval will come this year or next year. But, when approved, two new kinds of genes will become available to tackle bollworms.

Commercial Name	Bt Genes
Bollgard	Cry 1Ac
Bollgard II	Cry 1Ac + Cry 2Ab
VIPCot	VIP3
WideStrike	Cry 1Ac + Cry 1F

Roundup Ready Flex

Roundup Ready Flex™ from Monsanto is an improvement over the Roundup Ready® technology already in use singly and in conjunction with insect resistant genes in cotton. Some reports indicate that Roundup Ready applications caused reductions in yields due to boll abscission, because of a negative impact on anther development, pollen production, pollen morphology, pollen viability, and flower morphology. Monsanto's new Roundup Ready Flex™ (RR Flex) technology has been designed to enhance reproductive tolerance to glyphosate. The development of Roundup Ready Flex cotton varieties with a lengthened post-emergence-topical application window provides improved flexibility to treat past the 4-leaf growth stage when due to some reasons it was not possible to control weeds at an early stage. Experiments have shown that late application of Roundup Ready on the Roundup Ready transgenic cotton results in significant losses in yield due to direct damage to the plant. The Roundup Ready Flex can be sprayed as a post-emergence-topical application and will not cause any damage to the crop. Roundup Ready Flex can be sprayed on the Roundup Ready Flex cotton up to the 14 leaf stage and in two to three times higher quantities to control tougher weeds. The technology is close to approval.