Product Safety Assessment

WideStrike™ Insect Protection

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Names
- Cry1F
- Cry1Ac
- Bacillus thuringiensis proteins
- DAS-24236-5 X DAS-21023-5
- Bt proteins
- 281-24-236
- WideStrike™ Insect Protection
- WideStrike™
- 3006-210-23
- DAS-21023-5
- DAS-24236-5

Product Overview

- WideStrike™ Insect Protection is a combined insect-protection trait developed for use in cotton. WideStrike Insect Protection was developed by Dow AgroSciences LLC and utilizes the cry1F gene and cry1Ac gene in genetically modified cotton. Both genes express insecticidal proteins (called Cry1F and Cry1Ac) derived from different strains of a naturally occurring soil microorganism, Bacillus thuringiensis (Bt). For more information on Bt, Cry1F, and Cry1Ac, see Product Description. WideStrike Insect Protection offers a high level of protection against several economically significant insect pests including tobacco budworm, bollworm, pink bollworm, fall armyworm, loopers, and several other species listed in the Product Description.
- WideStrike Insect Protection provides season-long, whole-plant protection against insect feeding damage, which allows cotton plants to remain healthier throughout the growing season. Full-season protection against insect damage facilitates cotton varieties reaching their full genetic growing and yield potential. WideStrike Insect Protection can also increase farmers’ productivity by reducing various inputs (e.g., labor, fuel, equipment, pesticides) typically required for conventional insect control programs. For further details, see Product Uses & Regulatory Information.
- On the basis of rigorous testing and analysis of data on agronomic performance, disease and insect susceptibility, and compositional profiles of the seeds and fiber, regulatory agencies concluded that cotton with WideStrike Insect Protection is similar to conventional, non-transgenic cotton. The primary route of potential exposure occurs through ingestion. The proteins in WideStrike Insect Protection are present in common soil organisms, so exposure also can occur naturally but at much lower levels. The insecticidal proteins have no known effects on microorganisms, plants or animals (other than lepidopteran insects), including humans and livestock. For further details, see Exposure Potential and Health Information.
- Extensive safety data were provided by Dow AgroSciences to the U.S. Department of Agriculture (USDA), Environmental Protection Agency (EPA), and the Food and Drug Administration (FDA) before cotton with WideStrike Insect Protection was granted non-regulated status for cultivation in the USA. WideStrike Insect Protection subsequently was approved in 2009 for cultivation in Brazil.

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after review of safety data by the National Biosafety Technical Commission (CTNBio). For further details, see Environmental Information and Health Information.

**Manufacture of Product: Plant Transformation Process**

Plant biotechnology can be defined as a precise process in which scientific techniques (e.g., genetic modifications) are used to develop useful and beneficial plants with desirable “traits.” A trait refers to characteristics that are associated with the plant, including agronomic qualities and resistance to insects, herbicides, and disease. Plant biotechnology first identifies the genes responsible for the desired trait and then transforms them into plant cells. The trait may come from the plant itself (in this case cotton) or from a very specific gene of another organism, such as a bacterium.

DNA is the “genetic backbone” found in all microorganisms, plants, animals, and humans. Sequences of nucleotides (bases) in DNA encode the organisms' genes. Organisms that carry DNA introduced via genetic modification are referred to as transgenic, and the introduced DNA is termed a transgene. The first step in creating WideStrike™ cotton was the isolation and replication of DNA segments from different strains of *Bacillus thuringiensis* that were responsible for the expression of the desired insecticidal proteins (Cry1F and Cry1Ac). The isolated DNA fragments were then chemically re-synthesized to create the final transgenes, including plant-preferred DNA sequences that optimize expression of the insecticidal proteins in the plant.

As shown in Figure 1, a transgene is comprised of a protein coding region, a preceding promoter element, and a trailing regulatory element. The promoter element determines the strength at which a trait will be expressed in the plant. The promoter also determines in which plant tissues the trait will be expressed. The trailing regulatory element defines the length of the DNA to be expressed. WideStrike cotton is a stack of two independent transgenic events engineered with cry1F and cry1Ac genes. The Cry1F event is comprised of a cry1F protein coding region, the 4ocs Δmas promoter, and orf25 trailing regulatory element. The Cry1Ac event is comprised of a cry1Ac protein coding region, the maize ubiquitin-1 promoter, and orf25 trailing regulator element. It is critical that both Cry1F and Cry1Ac expressions are maintained at their optimal levels for the traits to exhibit their characteristics.

A “selectable marker gene” usually is associated with a gene of interest during plant transformation. Selectable marker genes can be used in both the laboratory and the field to quickly determine whether plants contain the desired genes and are expressing the desired proteins. For WideStrike Insect Protection, the pat gene is used as the selectable marker. (For more information on PAT, see Product Description.) The pat gene, which is located next to the cry1F gene and cry1Ac gene, is controlled by a different promoter, and the same bi-directional trailing regulatory element. The pat gene provides a certain level of tolerance to glufosinate-ammonium and facilitates the selection of plants containing Cry1F and Cry1Ac. However, the tolerance to glufosinate-ammonium herbicides provided by the pat gene in WideStrike™ Insect Protection is not equivalent to the glufosinate-ammonium herbicide tolerance of LibertyLink cotton.

**Fig. 1: Transgenes used to produce cotton with the WideStrike™ traits.**
After the transgenes were constructed, they were inserted into plant tissue through a process known as transformation. WideStrike™ Insect Protection was created through Agrobacterium-mediated transformation of cotton. Agrobacterium is a naturally occurring soil pathogen that can transfer and integrate selected DNA in a stable fashion into the cotton plant. Sections of immature cotton tissue (cotyledons) were incubated on artificial media with special strains of Agrobacterium that transferred the desired DNA into the cotton plant cells. Transformed cells were then isolated by growing plants on a selective medium, and transgenic plants subsequently were regenerated. Once integrated into the plant's genome, the transgene was inherited through normal sexual reproduction.

Each transformation experiment produced multiple events to identify the optimal balance between protein expression and agronomic quality of the cotton plant. For WideStrike cotton, the final events chosen during the “event sorting” process were known by the designation 281-24-236 (Cry1F) and 3006-21-23 (Cry1Ac). The two cotton events were combined through traditional plant breeding techniques to form cottonseed expressing the Cry1F and Cry1Ac proteins.

Numerous tests and checks are in place to ensure quality of the genetically modified seed and, ultimately, the generations of seed formed afterward. WideStrike cotton was extensively tested for the stability of the trait through several growing cycles, for safety to animals, humans, and the environment, and for retention of nutritional value.

Now that this process has proven successful, and WideStrike Insect Protection has been approved by the USDA, FDA, EPA, and CTNBio, as well as other regulatory agencies globally, the genetically modified material is sold to farmers to grow for production of fiber, cottonseed meal and hulls for livestock consumption, and cottonseed oil for human consumption. Successful development of genetically modified crops requires a deep understanding of the food chain, biology, regulatory requirements, and more.

**Product Description**

The product purchased by growers is seed cotton with WideStrike™ Insect Protection. Protection against insect pests is achieved by genetically modifying cotton plants to include two genes that express insecticidal proteins, rendering the cotton plants resistant to certain insect pests. The expression of the proteins (Cry1F and Cry1Ac) by the introduced genes (cry1F and cry1Ac) allows the plants to produce the same proteins produced by the naturally occurring soil bacterium from which the genes were isolated. Following is background information about each protein and its effects.

**Cry1F, Cry1Ac and Bt** – The cry1F gene, isolated from the common soil bacterium Bacillus thuringiensis var. aizawai (often referred to as Bt), produces the Cry1F protein. The cry1Ac gene (which produces the Cry1Ac protein) was isolated from a different strain of Bt (subsp. kurstaki). Bt was first discovered in 1901 by the Japanese biologist S. Ishiwatari as the source of disease that was killing large populations of silkworms. Bt was first used as an insecticide in 1920, and spray formulations containing either Bt bacteria or Bt proteins have been used for more than 40 years for crop protection, including Bt-based insecticides for organic farming operations. The development and use of EPA-registered Bt insecticides as an alternative to synthetic chemical insecticides expanded in the 1980s.

Beginning in the 1980s, the genes responsible for making Bt proteins were isolated and transferred into crop plants. In the United States, Bt was commercially approved first in transgenic cotton seed in 1995. Compared with conventional Bt spray formulations, transgenic plants expressing Bt proteins provide much more effective insect protection throughout the growing season. In addition to the Bt proteins Cry1F and Cry1Ac, other Bt proteins have been used to genetically modify commercial crops including potatoes, corn, and cotton.

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Bt proteins must be ingested to kill the insect. A susceptible immature insect (larva) eats the protein, which then binds to specific receptors in the larva's gut. Binding initiates a cascade of effects in the larva that ultimately leads to death.

Bt proteins are highly selective against certain groups and/or species of insects. The Cry1F and Cry1Ac proteins affect larvae of damaging lepidopteran (moth) species on cotton, including tobacco budworm (*Heliothis virescens*), bollworm (*Helicoverpa zea*), fall armyworm (*Spodoptera frugiperda*), southern armyworm (*Spodoptera eridania*), beet armyworm (*Spodoptera exigua*), pink bollworm (*Pectinophora gossypiella*), cabbage looper (*Trichoplusia ni*), soybean looper (*Chrysodeix includens*), saltmarsh caterpillar (*Estigmene acrea*), European corn borer (*Ostrinia nubilalis*), cotton leaf perforator (*Bucculatrix thurburiella*), omnivorous leafroller (*Platynota sulatana*), and citrus peelminer (*Marmagulosa*).

Cry1F and Cry1Ac proteins are expressed at effective concentrations throughout the growing season of WideStrike™ cotton. Targeted insect larvae are exposed to the insecticidal proteins when feeding on WideStrike plants at all stages in their life cycle. Thus, WideStrike cotton provides season-long protection against targeted pests.

Cry1F and Cry1Ac do not adversely affect beneficial insects or other organisms, including honey bees, earthworms, lady beetles, springtails, green lacewings, and beneficial predatory ants, beetles and wasps. For more information, see Environmental Information.

**PAT** – Phosphinothricin-N-acetyltransferase (PAT) is an enzyme isolated from the common soil bacterium *Streptomyces viridochromogenes*. Used as the “marker gene,” PAT imparts transgenic plants with a certain amount of tolerance to the herbicide glufosinate-ammonium and facilitates the selection of plants containing Cry1F and Cry1Ac. Glufosinate-ammonium was developed from the same bacterium as PAT and causes ammonia to build up in the plant tissues. Excess ammonia disrupts cell membranes and stops photosynthesis, which eventually kills the plants (either non-transformed cotton or certain species of weeds). PAT essentially is the antidote to glufosinate-ammonium, allowing the plant to detoxify the chemical. However, because the tolerance to glufosinate-ammonium herbicides provided by the pat gene in WideStrike™ Insect Protection cotton is not equivalent to the glufosinate-ammonium herbicide tolerance of LibertyLink cotton, the use of glufosinate-ammonium herbicides on WideStrike cotton is not labeled.

**Product Uses & Regulatory Information**

Cotton seed with WideStrike™ Insect Protection is used to produce high-quality cotton with greater efficiency by ensuring higher yields and less loss due to insect damage to the cotton plants. WideStrike Insect Protection also greatly reduces the number of pesticide applications usually required for common lepidopteran insect pests. WideStrike cotton may be used for production of fiber, cottonseed meal and hulls for livestock consumption, and cottonseed oil for human consumption. Regulations may exist that govern the manufacture, sale, transportation, use, and/or disposal of cotton with the WideStrike trait, especially if the seed is treated with an insecticide or fungicide. These regulations may vary by city, state, country or geographic region. Please review the product information for the specific product being used.
Exposure Potential

The Cry1F, Cry1Ac, and PAT proteins are present in common, non-pathogenic soil bacteria, so exposure occurs naturally and without concern. WideStrike™ cotton may be used for production of fiber, cottonseed meal and hulls for livestock consumption, and cottonseed oil for human consumption. Thus, consumers may wear or eat processed cotton products from cotton containing WideStrike™ traits. Moreover, none of the three expressed proteins are detectable in the oil, meal, and hulls of WideStrike cotton. Processed linters are composed of pure (>99%) cellulose and are treated with heat and solvent that remove and destroy residual protein. A number of studies have been done to demonstrate the human and animal safety of proteins used in WideStrike cotton. None of the proteins are associated with toxicity or allergenicity. See Health Information.

Farmers and cotton-gin workers may be exposed to harvested cotton products. Standard workplace procedures and precautions used when handling other cultivars of *G. hirsutum* should be followed when handling WideStrike cotton. See Health Information.

Health Information

On the basis of rigorous testing, WideStrike™ Insect Protection has received full food, feed, and environmental registration from regulatory agencies in the United States and Brazil. The US EPA found that there is reasonable certainty that no harm will result from exposure to the proteins in WideStrike Insect Protection cotton. Analysis of compositional profiles of the WideStrike seeds and fiber indicate that the profiles are similar to their non-transgenic parent counterparts and other cultivars of *G. hirsutum*. Cry1F, Cry1Ac, and PAT are present in soil bacteria and are not considered pathogens of humans or animals. None of the expressed proteins in WideStrike Insect Protection has biochemical characteristics or homology (relevant similarities) with known food allergens or toxins, indicating that WideStrike Insect Protection is highly unlikely to pose any risk of allergic reaction.

Acute mouse oral toxicity studies concluded that the three proteins expressed in WideStrike cotton do not pose any toxicological risk to human and animals. There are no differences in the nutrient composition of respective oil, meal, or hull products between WideStrike and conventional cotton. Poultry feeding studies have demonstrated no difference in body weight gains between chickens fed with WideStrike cottonseed meal and conventional cottonseed meal.

**Seed Treatments** - Agricultural seeds, including cotton with the WideStrike™ trait, may be treated with insecticides and/or fungicides, and these seed treatments can present certain risks. These potential risks are associated with the seed treatments and not the WideStrike traits. Consult the appropriate Safety Data Sheet and/or product label or tag for seed treatment hazard information, follow all directions for use, and wear all recommended personal protective equipment.

**Herbicide-Tolerant Traits** - Many cottonseed products with the WideStrike™ traits also have a trait that provides tolerance to herbicides such as glyphosate. Consult the appropriate product information sheets for the safety profile and precautions associated with such traits.

Environmental Information

Before a biotech product can be introduced to the market, review by appropriate governmental agencies is required. Using the criteria established by these agencies, Dow AgroSciences conducts extensive, validated studies for all of its biotech products. For the registration of cotton with the WideStrike™ traits in the United States, extensive safety and environmental data were generated and Trademark of The Dow Chemical Company ("Dow") or an affiliated Company of Dow

provided to the USDA, EPA, and also to the FDA as part of a pre-market consultation process. For the registration of cotton with the WideStrike™ traits in Brazil, extensive safety and environmental data were generated and provided to National Biosafety Technical Commission (CTNBio).

Cotton with the WideStrike traits produces minute quantities of the Cry1F and Cry1Ac proteins, contained in the plant and plant parts such as leaves, squares, flowers, and cottonseed. Both proteins degrade rapidly in the soil, minimizing the potential for run-off or exposure to soil-dwelling non-target organisms.

A number of non-target organisms were tested as part of the registration process for WideStrike Insect Protection, and no adverse effects were observed. Some of the organisms tested were honey bees, earthworms, lady beetles, springtails, green lacewings, and beneficial predatory ants, beetles, and wasps. No adverse effects were observed in birds or fish. In addition, there is very low risk for impact on Monarch butterflies, and none were observed in endangered species.

Another important environmental consideration with a biotech product is how cross-pollination will affect the environment. Cotton (Gossypium hirsutum) is mainly a self-pollinating plant, and the chance for gene exchange between cotton with the WideStrike trait and other cotton varieties, although possible, is minimal due to its physiological characteristics and various environmental/biological factors. In countries where cultivated, the risk of gene flow to plant species related to cotton (either under cultivation or wild) is very unlikely. There is no selective advantage for cotton varieties with WideStrike Insect Protection in the natural environment.

There is a potential long-term risk of target pest adaptation to the Cry1F and Cry1Ac proteins, which would lead to the possibility of reduced efficacy. Insect resistance management requirements are employed by WideStrike cotton growers to help mitigate this risk.

**Additional Information**

- Biotechnology Industry Organization "Commercial Status of Certain Agricultural Biotechnology Products" ([www.biotechrstatus.com](http://www.biotechrstatus.com))
- Expanded technical summary and additional references that support the information summarized here on WideStrike traits can be found in the GM Crop Database at the International Life Sciences Institute’s Center for Environmental Risk Assessment web site ([http://cera-gmc.org/index.php?action=gm_crop_database](http://cera-gmc.org/index.php?action=gm_crop_database))
- FDA Consultation Note to File ([http://www.fda.gov/default.htm](http://www.fda.gov/default.htm))
- CTNBIO Technical Decision for the Approval of WideStrike in Brazil ([http://www.ctnbio.gov.br/index.php/content/view/12886.html](http://www.ctnbio.gov.br/index.php/content/view/12886.html))

For more business information about WideStrike™ Insect Protection, visit the website for Dow AgroSciences.

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