Product Safety Assessment

Herculex® I Insect Protection

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- TC1507 (event number)

Product Overview

- Herculex® I Insect Protection is the first genetic trait in a new generation of insect protection traits for corn. Herculex I was developed in collaboration between Dow AgroSciences LLC and Pioneer Hi-Bred International, Inc. and utilizes the cry1F gene in genetically modified corn. The cry1F gene expresses an insecticidal protein (called Cry1F) derived from a naturally occurring soil micro-organism, Bacillus thuringiensis (Bt) var. aizawai. For more information on Bt and Cry1F, see Product Description. Herculex I offers a high level of protection from several economically important insect pests including European corn borer, southwestern corn borer, fall armyworm, black cutworm and western bean cutworm.

- Herculex I provides season-long, whole-plant protection from insect feeding damage, which allows corn plants to remain healthier and better fight off environmental stresses throughout the growing season. Full-season protection against insect damage and other stress factors allows corn hybrids to reach their full genetic growing potential. Thus, Herculex I protects and enhances yield potential for the corn hybrid. Herculex® I can also increase farmer’s productivity by reducing various inputs (e.g., labor, fuel, equipment, pesticides) typically required for conventional insect control programs.

- In addition to insect protection, corn hybrids with the Herculex I trait contain LibertyLink® technology which provides tolerance to glufosinate-ammonium herbicides by the expression of a protein generally referred to as PAT. (For more information see Product Description.) Corn plants possessing this tolerance can be directly sprayed after emergence with glufosinate-ammonium herbicides (e.g., LIBERTY® herbicide), allowing for broad spectrum weed control without herbicide damage to the corn plant. Benefits to the farmer are convenient and effective weed control that ultimately enhances yield potential for the corn.

- On the basis of rigorous testing, regulatory agencies concluded that corn with Herculex I Insect Protection is as safe as conventional, non-transgenic corn. Exposure occurs primarily by ingestion. The Cry1F and PAT proteins are present in common soil organisms, so exposure can also occur naturally but at much lower levels (see Exposure Potential and Health Information). Extensive safety data was provided by Dow AgroSciences LLC and Pioneer Hi-Bred International, Inc., to the U.S. Department of Agriculture (USDA), Environmental Protection Agency (EPA), Food and Drug Administration (FDA) and the regulatory systems of other countries before corn with Herculex I Insect Protection was approved for sale (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 corn) 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. 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 Herculex® I corn was the isolation and replication of DNA segments from *Bacillus thuringiensis* (var. aizawai) that were responsible for the expression of the desired insecticidal protein (Cry1F). The isolated DNA fragments were then chemically re-synthesized to create the final transgene, including plant-preferred DNA that optimizes expression of the insecticidal protein in the plant.

As shown in Figure 1, the transgene for Herculex® I *Insect Protection* is comprised of a protein coding region (expressing Cry1F), 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. In Herculex® I *Insect Protection*, the promoter (maize ubiquitin-1) and trailing regulatory (*Agrobacterium* Orf25) controls the Cry1F expression.

A "selectable marker gene" is normally 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 if plants contain the desired genes and are expressing the desired proteins. For Herculex® I *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 *cry*1F gene, is controlled by a different promoter and trailing regulatory. The *pat* gene provides tolerance to glufosinate-ammonium herbicides and facilitates the selection of plants containing Cry1F in the laboratory and field. It is critical that both Cry1F and PAT protein expressions are maintained at their optimal level in order for the trait to exhibit its characteristics in corn plants.

Fig. 1: Transgene used to produce corn with the Herculex I trait.
Numerous tests and checks are in place to ensure quality of the genetically modified seed and, ultimately, the generations of seed formed afterward. The Hercules® I corn 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 on all counts, and has been approved by the USDA, FDA and EPA as well as other regulatory agencies globally, the genetically modified material is sold to farmers to grow for human and animal consumption. Successful development of genetically modified crops requires a deep understanding of the food chain, biology, regulatory requirements and more.

Product Description
The product that is purchased is seed corn with Herculex I Insect Protection. The protection is achieved by genetically modifying the corn to include two genes which express proteins, making it resistant to certain insect pests and tolerant to certain herbicides. The expression of the new proteins (Cry1F and PAT) by the new genes (cry1F and pat) allows the plants to produce the same proteins as those produced by the naturally occurring soil bacteria from which the genes were isolated. Following is background information about each protein and their effects.

Cry1F and Bt – The cry1F gene, isolated from the common soil bacterium Bacillus thuringiensis var. aizawai (often referred to as Bt), produces the insect control protein. 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 organic farming operations. EPA-approved Bt insecticides saw expanded use and development in the 1980s as an alternative to synthetic chemical insecticides.

Beginning in the 1980’s, the genes responsible for making Bt proteins were isolated and transferred into corn plants. Bt was commercially approved in transgenic corn seed in the mid-1990s. Compared to conventional Bt spray formulations, transgenic plants with the Bt protein provide much more effective insect protection throughout the growing season. Other Bt proteins besides Cry1F have been used to genetically modify potatoes, cotton, and other types of commercial corn.

Bt 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 on only certain categories and/species of insects. The Cry1F protein affects the larvae of damaging lepidopteran (moth) species that include corn borers (European corn borer, southwestern corn borer, lesser corn stalk borer, sugarcane borer and southwestern corn stalk borer), black cutworm, western bean cutworm, fall armyworm and to some degree the corn earworm. These insects can destroy significant percentages of agricultural crops if left untreated. For example, the European corn borer is estimated to cause $1-2 billion of damage to corn each year.

Damage from these insects can also allow fungi to grow on the corn which can be harmful to animals or humans. Available data show that corn hybrids expressing Bt Cry toxins have reduced vulnerability to mycotoxin-producing fungi, thereby enhancing the safety of the grain for livestock feed and for human food.

The Cry1F protein is expressed at effective concentrations throughout all the plant’s parts in Herculex I corn. Because the tissues of the Herculex I plants express the Cry1F protein, the targeted larvae are exposed to the insecticidal protein at all stages in their life cycle. Thus, Herculex I provides season-long protection against targeted pests.

Cry1F has been found to not adversely affect beneficial insects or other organisms, including honeybees, earthworms, lady beetles, springtails and green lacewings, or the Monarch butterfly or endangered species. 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 tolerance
to glufosinate-ammonium, the active ingredient in herbicide products such as Liberty® herbicide. Corn with Herculex® I Insect Protection can be sprayed with this herbicide to control weeds with no crop loss.

Glufosinate-ammonium was developed from the same bacteria as PAT and causes ammonia to build up in the plant tissues. Excess ammonia disrupts cell membranes and stops photosynthesis. Eventually the plant, preferably a weed, dies. PAT is essentially the antidote to the herbicide, allowing the plant to detoxify the active ingredient in this particular herbicide. When PAT is produced by the crop, in this case corn, the herbicide targets only the weeds without detriment to the crop.

**Product Uses**

Corn seed with Herculex I Insect Protection is used to produce high quality corn with greater efficiency for higher yields, and less loss due to insects. It reduces the need for pesticide applications and has the potential to lower the likelihood of fungus-produced mycotoxins accumulating in the kernels.

**Exposure Potential**

The Cry1F and PAT proteins are present in common, non-pathogenic soil bacteria, so exposure can occur naturally and without concern. Exposure to Herculex I Insect Protection, however, occurs mainly through ingestion of corn. Greatest exposure potential to genetically modified corn will involve farmers. Because harvested corn with Herculex I Insect Protection is as safe as corn without it, standard farm workplace procedures and precautions should be followed. See Health Information.

Consumers and animals eat processed corn products that may contain the Cry1F and PAT proteins. Several studies have demonstrated the safety of Cry1F and PAT proteins for human and animal consumption. Neither protein is associated with toxicity or allergenicity. See Health Information.

**Health Information**

On the basis of rigorous testing, regulatory agencies concluded that corn with Herculex I Insect Protection is as safe as non-transgenic corn. The Herculex® I trait has received full food, feed and environmental approval by the United States, Canada and Argentina. It has been approved for import by the respective regulatory bodies in Japan, Australia, New Zealand, South Korea, South Africa, Taiwan, China, Mexico and the Philippines. Approvals are currently pending in other countries such as those in the European Union, Russia and Switzerland.

The EPA found that Herculex I and all Bt lepidopteran-resistant corn products do not pose risks to human health. Both Cry1F and PAT are present in soil bacteria and are not considered as pathogens for humans or animals. Neither Cry1F nor PAT has biochemical characteristics or homology (relevant similarities) with known food allergens or toxins, indicating that Herculex I Insect Protection is highly unlikely to pose any risk of allergic reaction.

Healthy mice demonstrated lack of acute toxicity after ingesting a dose of Cry1F or PAT protein many thousand times the estimated dietary intake of humans. Nutrients like fat, protein, fiber, minerals and vitamins were measured and no significant difference between corn with the Herculex I trait and the non-transgenic corn was found. Some variances of nutrients such as linoleic and linolenic acids were noted, however all values for nutrients remained within the normal range of variation reported for maize grain.

A chicken broiler study has been conducted on grain harvested from Herculex I hybrids. No differences in nutritional quality or growth of the broilers were observed between those animals that consumed the Herculex® I Insect Protection corn and those that were fed conventional corn.

**Seed Treatments.** Agricultural seeds, including corn with the Herculex I trait, may be treated with an insecticide and/or a fungicide and these seed treatments can present certain health risks. These risks are associated with the seed treatments and not the Herculex I trait. Consult the appropriate Safety Data Sheet (SDS) and/or label or tag for seed treatment hazard information, and wear all recommended personal protective equipment.
Environmental Information

Before a biotech product can be introduced to the market, approval by appropriate governmental agencies is required. Using the criteria established by these agencies, Dow AgroSciences conducts extensive, validated tests for its biotech products. For the approval of corn with the Herculex® I trait, extensive safety data was provided to the USDA, EPA, and FDA as part of a pre-market consultation process and to the regulatory agencies of other countries.

The corn with the Herculex I trait produces minute quantities of the Cry1F protein, contained in the plant and plant parts such as pollen, roots, and leaves. Cry1F protein degrades 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 Herculex I Insect Protection and no adverse effects were observed. Some of the organisms tested include honeybees, earthworms, lady beetles, springtails and green lacewings. No adverse effects were observed in birds or fish. In addition, the EPA found that “scientific evidence demonstrates that Bt corn does not impact monarch butterfly populations,” and that these products have no effects on endangered species.

Another important environmental consideration with a biotech product is how cross-pollination will affect the environment. Gene exchange between corn with Herculex I trait and other cultivated corn varieties can occur. The exchange will be similar to that which occurs naturally between cultivated corn varieties at the present time. In the U.S. and Canada or other countries where Herculex I Insect Protection is approved for cultivation (Argentina, Japan), where there are no plant species closely related to corn in the wild, the risk of gene flow to other species is unlikely. There is no selective advantage for corn hybrids with Herculex® I Insect Protection in the natural environment.

There is a potential long-term risk of target pest adaptation to the Cry1F protein leading to the possibility of reduced efficacy. An insect resistance management plan is in place with growers to mitigate this risk.

Regulatory Information

Regulations may exist that govern the manufacture, sale, transportation, use, and/or disposal of corn with Herculex I 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 SDS and product label for the product you are using.

Additional Information

- Dow AgroSciences Herculex Insect Protection web site (http://www.dowagro.com/herculex)
- Expanded technical summary and additional references that support the information summarized here on Herculex/TC1507 can be found at Agbios web site (http://www.agbios.com/dbase.php?action=ShowProd&data=TC1507&frmat=LONG)
- www.cropcomposition.org
- USDA notice of deregulation (http://www.aphis.usda.gov/brs/aphisdocs2/00_13601p_com.pdf)
- FDA Consultation Note to File (http://www.cfsan.fda.gov/~rdb/bnfm073.html)

For more business information about Herculex I Insect Protection, visit the Dow AgroSciences web site.

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