

Determination of the Safety of Monsanto's
Cotton MON 88913 (Herbicide Tolerant Cotton)
for Direct Use as Food, Feed and for Processing

Food and Feed Safety:

The product dossier on RR Flex Cotton were reviewed for safety and nutritional differences compared with the conventional corn. The focus of the review was on any new or altered expression trait and changes in composition and nutritional content or value relative to the conventional corn. At the end of the safety assessment, a conclusion was made that the RR Flex Cotton is as safe as the conventional corn taking into account dietary impact of any changes in nutritional content or value.

A biosafety permit for RR Flex Cotton and all progenies derived from crosses of the product with any conventionally-bred corn and corn containing approved-biotech events for direct use as food, feed and for processing was issued to Monsanto Philippines Inc. on November 29, 2005. The permit is valid for five years and shall expire on November 28, 2010 subject to the terms and conditions set forth in DA Administrative Order No. 8, Series of 2002. The said Cotton event was included in the Lists of Approval Registry (Delisting) being prepared by the Department of Agriculture- Bureau of Plant Industry.

This approval is for direct use as food, feed and for processing only. This does not include cultivation of RR Flex Cotton in the Philippines. Food and Feed use of RR Flex Cotton and its by-products is therefore authorized as of November 29, 2005. The Biosafety Permit (No. 05-021) stated that "Glyphosate Herbicide-Tolerant RR Flex Cotton is as safe for human food, livestock feed and for processing as its conventional counterparts".

I. Brief Identification of the Genetically Modified Organism (Living Modified Organism)

Designation: Cotton 88913 (RR Flex Cotton)

Applicant: MONSANTO PHILIPPINES INC.
7th Floor, Ayala-FGU Center
Alabang-Zapote Rd., cor Acacia Avenue
Madrigal Business Park
Alabang 1770 Muntinlupa City
Philippines

Plant Species:

Name: Cotton (*Gossypium hirsutum* L.)

Parent Material: Cotton variety Coker 312.

Center of Origin:

The most important agricultural cottons are *G. hirsutum* and *G. barbadense*. These are both allotetraploids of New World origin and presumably of ancient cross between Old World A Genomes and New World D genomes. Wild diploid species occur in Australia, the Afro-Arabia and America. Wild tetraploid species

occur in the New World (Hawaii, Northeastern Brazil, Galapagos, Mexico, Antilles and certain Pacific Islands, South and Central America, coast of Peru, Ecuador and Galapagos Island, Middle America, West Indies, Polynesia, North Africa, tip of Florida). The wild populations of *G. hirsutum* are relatively rare and tend to be widely dispersed.

Toxic Factors/Allergen(s):

Cotton oil is used for human consumption and there is very little protein in the oil, cottonseed oil is not a potential source of allergens. Aflatoxins and gossypol are present in the cotton seeds. Gossypol is naturally occurring in the cottonseed while aflatoxin is a fungal secondary metabolite which accumulates during fungal infection

Trait Description:

Herbicide (glyphosate) tolerance

Trait Introduction Method:

Agrobacterium mediated transformation

Donor Organism:

Agrobacterium sp. Strain CP4, source of *cp4 epsps* gene which confers tolerance to herbicide (glyphosate).

Pathogenicity:

There have been no reports of adverse effects on *Agrobacterium* sp., a naturally occurring bacterium encoding for a CP4 EPSPS protein on human and animals. CP4 EPSPS, being not from a known allergenic source, has a long history of safe use in human and animal consumption.

Proposed Use:

For direct use as food, feed or for processing

II. Background Information

Four species of the genus *Gossypium* are known as cotton, which is primarily for the fiber produced from the seed coat trichomes that is made into textiles. Cotton is the leading plant fiber crop produced in the world and the most important in the U.S. In the U.S., commercial cotton has a long history of agricultural production. Cotton production in the U.S. is located primarily in a region including 17 southern states across the cottonbelt, which extends across the southern and western U.S. from Virginia south and west to California. In addition to cotton lint, cottonseed meal and oil are produced as valuable byproducts. Cottonseed is also used in manufacturing cottonseed oil as a premium quality oil used for a variety of food uses, including frying oil, salad and cooking oil, mayonnaise, salad dressing, shortening, margarine, and packing oil.

On June 27, 2005, Monsanto Philippines Inc. submitted an application to the Bureau of Plant Industry requesting for biosafety permit under AO#8 part 5 for RR Flex Cotton which has been genetically modified for herbicide resistance.

Monsanto Philippines, Inc. has provided data on the identity of RR Flex cotton, a detailed description of the transformation method, data and information on the gene insertion sites, copy number and levels of expression in the plant, the role of the inserted genes and regulatory sequences in donor organisms and full nucleotide sequences. The novel proteins were identified, characterized and

compared to the original bacterial proteins, including an evaluation of their potential toxicity to livestock and non-target organisms. Relevant scientific publications were supplied.

RR Flex Cotton has been evaluated according to BPI's safety assessment by concerned agencies: [(Bureau of Animal Industry (BAI), Bureau of Agriculture, Fisheries and Product Standards (BAFPS)] and Scientific Technical Review Panel (STRP). The process involves an intensive analysis of the nature of the genetic modification together with a consideration of general safety issues, toxicological issues and nutritional issues associated with the modified cotton.

The petitioner/applicant published the said application on two widely circulated newspapers (The Manila Times and Malaya) on August 5, 2005 for public comment/review. BPI did not receive any comment on the petition during the 30-day comment period.

Review of results of evaluation by the BPI Biotech Core Team in consultation with DA-Biotechnology Advisory Team (DA-BAT) completed the approval process.

III. Description of Novel (Introduced) Traits

Cotton MON 88913 is a second-generation glyphosate-tolerant cotton product, which provides increased tolerance to glyphosate relative to the current product, Roundup Ready cotton event 1445, (herein referred to as Roundup Ready cotton), to provide more effective and flexible weed control options during production.

Control of weeds in a cotton crop is essential because weeds compete with the crop for the same limited resources in the field including sunlight, water and nutrients. Use of a Roundup agricultural herbicide in a crop provides an efficient and cost-effective means of controlling weeds.

Using modern biotechnology, Monsanto Company has developed Roundup Ready® Flex Cotton plants (*Gossypium hirsutum* L.) that are tolerant to glyphosate. The genetically modified cotton plant was produced by the introduction of: the *cp4 epsps* gene derived from the common soil bacterium *Agrobacterium* strain CP4 which encodes for the production of the CP4 EPSPS enzyme. The gene product is responsible for conferring tolerance to glyphosate.

RR Flex cotton plants produce the CP4 5-enolpyruvylshikimate-3-phosphate synthase protein (CP4 EPSPS) derived from *Agrobacterium* strain CP4. The CP4 EPSPS is naturally less sensitive to inhibition by glyphosate and has been shown to impart tolerance to glyphosate in several crops. CP4 EPSPS confer glyphosate tolerance to cotton plants containing these proteins.

Glyphosate, the active ingredient in Roundup® agricultural herbicides, kills plants by inhibiting the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS). This enzyme is a critical step in the shikimic acid pathway for the biosynthesis of aromatic amino acids in plants and microorganisms, and its inhibition leads to the lack of growth in plants. The aromatic amino acid biosynthetic pathway is not present in mammalian, avian or aquatic animals. This explains the selective activity in plants and contributes to the low risk to human health and the environment from the use of glyphosate according to label directions.

Safety of Expressed Proteins

The CP4 EPSPS protein is from *Agrobacterium* sp. CP4 strain, a common soil bacterium. The bacterium does not encode for any known pathogenic or allergenic proteins.

The CP2EPSPS proteins are functionally similar to a diverse family of EPSPS proteins typically present in food and feeds derived from plant microbial sources. EPSPS proteins are found ubiquitously in all plant-derived foods. The amino acid sequence of CP4EPSPS and other EPSPS proteins found in food are comparable. The CP4 EPSPS proteins have no known similarity with known protein toxins; CP4 EPSPS are not stable to heat or processing. The CP4 EPSPS is rapidly degraded by proteolytic enzymes (digestibility *in vitro*), limiting the exposure of the GIT and less likelihood that the protein can exert pharmacological, toxic or allergic effects.

The CP4 EPSPS protein is non-toxic and non-allergenic based on comparative analysis of their amino acid sequences to known protein toxins and allergens using specific bioinformatics tools.

IV Nutritional Composition (Compositional Analysis)

Under the same agronomic condition as conventional counterpart cotton, MON 88913 was found to be nutritionally equivalent to cotton that does not contain the *cp4 epsps* coding sequence or produce the CP4 EPSPS protein, and to the general population of commercial conventional cotton. CP4 EPSPS protein has no effect on the key nutrients. Values were well within the range.

V. Anti-Nutritional Factors

The cyclopropenoid fatty acids – malvalic acid, dihydrosterculic acid, and sterculic acid – are anti-nutrients found in cottonseed and cottonseed oil. Levels of cyclopropenoid fatty acids were measured in MON 88913 cottonseed, cottonseed meal, cottonseed oil and compared to MON 88913(-) cottonseed, meal and oil. No statistical differences were observed in cyclopropenoid fatty acid content between MON 88913 and MON 88913(-) cottonseed, meal, or oil in the combined site analyses.

The data support the conclusion that seed, meal and oil derived from Roundup Ready Flex Cotton MON 88913 are compositionally equivalent to those derived from cotton varieties grown commercially today.

VI. Regulatory Decision

After reviewing the scientific data and information relevant to the application of Monsanto Philippines Inc., it is concluded that RR Flex Cotton and all progenies derived from crosses of the product with any conventionally-bred cotton, and cotton containing approved-biotech events for direct use as food or feed or for processing is as safe and substantially equivalent to its unmodified counterpart, and is therefore approved for direct use as food, feed and for processing. Monsanto shall duly inform the public of this approval by way of publishing in any one (1) of the top three (3) leading newspapers in the country that imports of this product is covered by conditions for approval as provided in Department of Agriculture Memorandum Circular No. 8, Series of 2003.