

Determination of the Safety of Monsanto's
Corn GA 21 (Herbicide Tolerant Corn)
for Direct Use as Food, Feed and for Processing

Food and Feed Safety

The product dossier on Corn GA 21 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 Corn GA 21 is as safe as the conventional corn taking into account dietary impact of any changes in nutritional content or value.

A biosafety permit for Corn GA 21 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 or for processing was issued to Monsanto Philippines Inc. on November 20, 2003. The permit is valid for five years and shall expire on November 19, 2008 subject to the terms and conditions set forth in DA Administrative Order No. 8, Series of 2002. The said corn event (Corn GA 21) will be 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 Processing only. This does not include cultivation of Corn GA 21 in the Philippines. Food and Feed use of Corn GA 21 and its by-products is therefore authorized as of November 20, 2003. The Biosafety Permit (No. 03-009) stated that "Herbicide(Glyphosate)-Tolerant Corn GA 21 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:	Corn GA 21 (Glyphosate tolerant corn)
Applicant:	MONSANTO PHILIPPINES INC. 7 th Floor, Ayala-FGU Center Alabang-Zapote Rd., cor Acacia Avenue Madrigal Business Park Alabang 1770 Muntinlupa City Philippines
Plant Species:	
Name:	Corn (<i>Zea mays</i> L.)
Parent Material:	Inbred corn lines produced by Monsanto
Center of Origin:	Mexico, Central America and South America
Toxic Factors/Allergen(s):	Trypsin inhibitor, phytic acid, and secondary metabolites such as raffinose, ferulic acid and p-coumaric acid are present in low amount, 2,4-dihydroxy-7-methoxy-2H-1,4-benzoxazin-3(4H)-1

(DIMBOA) is a potential toxicant but declines rapidly as the plant grows

Trait Description: Herbicide Tolerance

Trait Introduction Method: Biolistic (Particle acceleration method)

Donor Organism: *Zea mays* L. a source of *mepsps* gene

Pathogenicity: Corn grain is a source of food for humans and animals and industrial applications for thousand of years. Animals consume silage that derives 50% of its nutritional value for grain. Corn as a food source for humans and animals has a history of safe use.

In an unprocessed form, corn has proven safe as both human food and animal feed. Corn contains only low levels of the natural antinutrient trypsin and chymotrypsin inhibitors. The most common toxicant associated with corn is the mycotoxins, which are produced by fungi that grow on corn kernels and not by the corn itself.

Proposed Use: For direct use as food, feed and for processing

II. Background Information

On May 6, 2003, Monsanto Philippines Inc. submitted an application to the Bureau of Plant Industry (BPI) requesting for Biosafety Permit under Administrative Order Number 8 Part 5 for corn event Corn GA 21 which has been genetically modified for herbicide tolerance.

Roundup Ready corn was developed by Monsanto Company and DEKALB Genetics Corporation. The genetically modified corn plants are tolerant to glyphosate. Roundup Ready corn event GA21 was produced by the introduction of a modified corn 5-enolpyruvylshikimate-3-phosphate synthase (*mepsps*) gene from corn (*Zea mays*). 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.

Monsanto Philippines, Inc. has provided data on the identity of Corn GA21, 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.

Corn GA 21 has been evaluated according to BPI's safety assessment by concerned agencies {Bureau of Animal Industry (BAI), Bureau of Bureau of Agriculture, Fisheries and Product Standards (BAFPS)} and a 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 corn.

The petitioner/applicant published the said application on two widely circulated newspapers (Malaya and The Daily Tribune) on June 7, 2003 for public comment/review. BPI received no 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

Corn GA 21 (Trade name: Roundup-Ready Corn) and all corn lines/hybrids derived from this event contain the EPSPS coding sequence from *E. coli*. The EPSPS gene codes for the synthesis of EPSPS enzyme, which is involved in the shikimic pathway for aromatic amino acid biosynthesis in plants and microorganisms (Steinrücken and Amrhein, 1980). The shikimic is not present in animals, which contributes to the selective toxicity of glyphosate to plants. The modified corn *epsps* (*mepsps*) gene is completely sequenced and encodes a 47.7 kD protein consisting of 445 amino acids. It differs from wild-type corn EPSPS by two amino acid substitutions. This results in a protein with greater than 99.3 % sequence identity to that of the corn protein. The *mepsps* protein and the wild type EPSPS from corn are immunologically and functionally equivalent, except for their affinity to glyphosate, as anticipated by high sequence similarity.

The plant transformation vector used to produce Roundup Ready Corn Event GA21 was plasmid pDPG434. The DNA segment used in the transformation contained the *mepsps* gene and its expression components. The *Not* I fragments contain the *mepsps* gene under the regulation of the rice actin promoter and rice actin intron and contain the nos3' polyadenylation sequence. The *mepsps* coding sequence is fused to the optimized transit peptide (OTP) coding sequence (*otp*). The OTP directs the *mepsps* protein to the chloroplast, the location of the native EPSPS in plants and the site of aromatic amino acid biosynthesis. Transit peptides are typically cleaved from the "mature" protein following delivery to the plasmids (della-Cioppa *et. al.*, 1986).

Safety of the Expressed Proteins

The safety assessment of the mEPSPS protein produced in RR corn event GA21 established that there were no indications of toxicity of the protein. Oral administration of the protein in mice presented no adverse effects in mice. Moreover, the mEPSPS protein did not show meaningful amino acid sequence similarity when compared to known protein toxins present in the PIR, EMBL, SwissProt, and GenBank protein databases.

Furthermore, the comparison of the amino acid sequence of the mEPSPS protein and known protein allergens using a series of public domain genetic databases did not show any allergenic concern. No biologically significant sequence similarities were observed between the mEPSPS protein and any of the allergens described in the databases. In addition, the protein and its enzymatic activity is rapidly degraded in simulated human gastric and intestinal fluids comparable to other safe dietary proteins.

IV. Nutritional Composition (Compositional Analysis)

Extensive compositional analyses of corn seed and forage establish that the levels of proximate components (protein, fat, ash, carbohydrate, moisture), acid detergent fiber (ADF) and neutral detergent fiber (NDF) and phosphorus in the grain and forage of Roundup Ready corn line GA21 were comparable to those in the grain and forage of the control, conventional line. RR corn GA21 is substantially similar to other commercial varieties of corn that are currently available, except for tolerance to glyphosate. This is based on evaluation of phenotypic characteristics, homology of the

expressed protein to endogenous corn EPSPS and the lack of any deleterious environmental fate or effects.

The compositional analyses and established poultry feeding studies taken together demonstrate that the composition and feeding value of Roundup Ready corn GA21 is equivalent to conventional corn. Moreover, established studies on swine and feedlot cattle performances demonstrate that the composition and feeding value of herbicide-tolerant corn GA21 is also equivalent to conventional corn. Pigs and steer fed with genetically modified corn had similar carcass characteristics to pigs fed with conventional corn. Also, these groups of pigs and steers had no significant differences in moisture, protein, fat, and ash in muscles.

Together with safety data of the introduced protein, mEPSPS, it is concluded that Roundup Ready corn is as safe and nutritious as conventional corn for food and feed use.

V. Anti-Nutritional Factors

Few anti-nutrients have been established to occur in corn, which has no relevance to its food use. Though trypsin inhibitor, phytic acid, and secondary metabolites such as raffinose, ferulic acid and p-coumaric acid have been established as anti-nutrients in corn, they are present in very low amount and are below the thresholds considered to raise a food safety concern. The amount of anti-nutrients present in Roundup Ready corn GA21 fell within the range found in non-transgenic corn.

VI. Regulatory Decision

After reviewing the scientific data and information relevant to the application of Monsanto Philippines, Inc., it is concluded that Corn GA 21 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 is as safe and substantially equivalent as 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.