

Determination of the Safety of Monsanto's
Combined trait product corn: MON 810 x NK 603
for Direct Use as Food, Feed, and Processing and for Propagation

Food and Feed and Environmental Safety

The product dossiers on Monsanto's Combined trait product corn: MON 810 x NK 603 were reviewed for safety and nutritional differences compared with the conventional corn. The focus of the food/feed safety and environmental assessment is based on five major issues/concerns regarding stacked genes from different sources namely a) gene interaction; b) effect on metabolic pathways; c) differential gene expression due to stacking; d) field performance and e) agricultural management.

A biosafety notifications for combined trait product corn: MON 810 x NK 603 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 and for propagation were issued to Monsanto Philippines Inc. on November 16, 2004 and July 19, 2005 respectively. The notifications are valid for five years and shall expire on November 15, 2009 and July 18, 2010 subject to the terms and conditions set forth in DA Administrative order No. 8, Series of 2002, and Memorandum Circulars Nos. 6 and 8, Series of 2004. The said combined trait product was included in the Lists of Approval Registry (Delisting) being prepared by the Department of Agriculture-Bureau of Plant Industry.

This approval is for use as Food, Feed and Processing only. This also includes cultivation of combined trait product corn: MON 810 x NK 603 in the Philippines. Food and Feed use and Cultivation of combined trait product corn: MON 810 x NK 603 its by-products is therefore authorized as of November 16, 2004 and July 19, 2005. The biosafety notifications for direct use (No. 04-002) and for propagation (05-001) stated that combined trait product corn: MON 810 x NK 603 is as safe for human food, livestock feed and for processing as its conventional counterparts and safe for the environment".

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

Designation: Combined trait product corn: MON 810 x NK 603

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

Plant Species:

Name: Corn (*Zea mays* L.)

Parent Material: Inbred corn lines (and/or isolines) developed and 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)-one (DIMBOA) a potential toxicant but declines rapidly as the plant grows
Trait Description:	Insect resistance and herbicide tolerance
Trait Introduction Method:	Conventionally breeding
Donor Organisms:	<p><i>Bacillus thuringiensis</i> var <i>kurstaki</i>, strain HD-1 (<i>Btk</i>), a widely distributed, non-pathogenic, sporulating, Gram positive bacteria, the source of the <i>cryIAb</i> gene which produces a crystal protein effective as an insecticide against Lepidopteran insects.</p> <p><i>Agrobacterium</i> sp.CP4, which encodes for the naturally occurring glyphosate-tolerant EPSPS protein.</p>
Pathogenicity:	<p><i>Bacillus thuringiensis</i> var. <i>kurstaki</i> has been shown to be non-toxic to humans, other vertebrates and beneficial insects. <i>B.t.k.</i> based foliar insecticides have been registered for over 30 years and have a long history of safe use. The toxin produced by the <i>cryIAb</i> gene is known to act specifically on the gut of lepidopteran insects. There are no receptors for the protein Cry1Ab on mammalian intestinal cell surfaces and humans are not susceptible to this toxin. Additionally, Cry1Ab denatures at elevated temperatures during food processing and rapidly degrades in the soil.</p> <p>The <i>cp4 epsps</i> gene was derived from the common soil bacterium <i>Agrobacterium</i> sp. Strain CP4 which encodes for the naturally occurring glyphosate-tolerant CP4 EPSPS protein. No other protein is known to be produced which may bring about toxicity, allergenicity or may be anti-nutritional in nature. No known pathogenicity in humans and animals because of the absence of the shikimic acid pathway in animals.</p>
Proposed Use:	For direct use as food, feed or for processing and for propagation

II. Background Information

Monsanto Philippines, Inc. has filed an application with attached technical dossiers to the Bureau of Plant Industry on July 16, 2004 and on March 10, 2005 for a biosafety notifications for direct use as food, feed and for processing and for propagation respectively under Administrative Order (AO) No. 8 Part 5 for Combined trait product corn: MON810 x NK603 which has been genetically modified for insect resistance and herbicide tolerance.

A safety assessment of combined trait product corn: MON 810 x NK 603 was conducted as per Department of Agriculture Administrative Order No. 8 Series of 2002. The focus of risk assessment is the gene interactions between the two transgenes.

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 MON 810 with resistance to Lepidopteran pests are produced through introduction of the *cry1Ab* gene from *Bacillus thuringiensis* subsp. *kurstaki*. The *cry1Ab* sequence encodes for the production of a Bt insect toxin.

Corn NK 603 with tolerance to the family of Roundup® herbicides are produced through introduction of the *cp4 epsps* gene from *Agrobacterium* sp. Strain CP4. The *cp4 epsps* sequence encodes for the production of the naturally occurring 5-enolpyruvylshikimate-3-phosphate synthase.

Inbred line, MON 810, was crossed with inbred line, NK 603, resulting in the combined trait product MON 810 x NK 603 with resistance to insects and tolerance to the herbicide glyphosate.

Safety of the Expressed Proteins

Without stacking, both the insertion of *cry1ab* and *cp4 epsps* in corn did not result in the occurrence of a new allergen or a new toxin. The modes and sites of biological activity are significantly different for CP4 EPSPS and Cry1Ab and there is no known or conceivable mechanism of interaction between these proteins leading to adverse health effects in animals or man. Both Cry1Ab and CP4 EPSPS are non allergenic proteins because both these novel proteins could easily be digested by simulated gastric and intestinal fluids. Furthermore, using bioinformatics tools, both novel proteins do not share any significant homology or amino acid sequence.

CP4 EPSPS protein in NK 603 and Cry1Ab protein in MON 810 were considered to have no effect on normal plant metabolism were a safety assessment was conducted for each event and the subsequent approvals were granted. Expression of Roundup Ready® and Yieldgard® Corn Borer traits in the stacked trait F1 hybrids is not expected to produce interactive or synergistic effects on plant metabolism because different modes of action and binding sites are involved.

- a) CP4 EPSPS and Cry1Ab proteins have different modes of action.
- b) CP4 EPSPS is directed to the chloroplasts while Cry1Ab accumulates in the cytoplasm.

No possible interaction effect is expected due to entirely different modes and sites of biological activity of the two stacked gene products, thus no effect on stability and expression level of either one of the genes.

IV. Nutritional Composition (Compositional Analysis)

The World Health Organization (1995) stated that two plants that are substantially equivalent to conventional varieties are crosses by conventional breeding techniques; the combined trait product is expected to be substantially equivalent to the single event products.

V. Anti-Nutritional Factors

No known anti nutritional factors for individual events. Thus, MON 810 x NK 603 has no known anti nutritional factors.

VI. Environmental Assessment

The field performance of the stacked plant is equivalent to the relevant field performance of the individually approved transformation events. The agronomic characteristics of stacked plant are

equivalent to the agronomic characteristics of the individually approved transformation events. The presence of the traits will not cause a change in cultural management of crop except for the intended changes

VII. Regulatory Decision

After reviewing the scientific data and information relevant to the combined trait corn MON 810 x NK 603 application of Monsanto Philippines Inc. it is concluded that no interaction found between/among the stacked traits, hence this plant product was found to be as safe as its conventional corn and can substitute for its traditional counterpart for direct use as food, feed and for processing and for propagation and is therefore approved for direct use as food, or feed or for processing and for propagation. Monsanto is hereby notified that it may proceed with the activities for the above product for direct use as food and feed or for processing and for propagation following all existing rules and regulations consistent with DA AO #8.