

Determination of the Safety of Monsanto's
Corn NK 603 (Glyphosate-Tolerant Corn)
for Direct Use as Food, Feed and for Processing and for Propagation

Food and Feed and Environmental Safety

The product dossiers on Corn NK 603 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 NK 603 is as safe as the conventional corn taking into account dietary impact of any changes in nutritional content or value and Corn NK 603 is safe to humans, animals and non-target organisms and as nutritious as ordinary corn.

A biosafety permit for Corn event 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 and for processing was issued to Monsanto Philippines Inc. on September 22, 2003. The permit for direct use is valid for five years and shall expire on September 21, 2008 subject to the terms and conditions set forth in DA Administrative Order No. 8, Series of 2002. A biosafety permit for propagation of Corn NK 603 was also issued to Monsanto Philippines, Inc. on February 8, 2005. The permit for propagation is valid for five years and shall expire on February 7, 2010 subject to the terms and conditions set forth in DA Administrative Order No. 8, Series of 2002. The said corn event (NK 603) was included in the Lists of Approval Registry (Delisting) for direct use and also for propagation being prepared by the Department of Agriculture-Bureau of Plant Industry.

This approval is for use as Food, Feed and Processing as well as for cultivation of Glyphosate-Tolerant Corn NK 603 in the Philippines. Food, Feed and use of its by-products is therefore authorized as of September 22, 2003 and cultivation is authorized as of February 8, 2005. The biosafety permit for direct use as food feed and for processing (No. 03-003) and biosafety permit for propagation (No. 05-0002) stated that "Glyphosate-tolerant Corn NK 603 is as safe for human food, livestock feed and for processing as its conventional counterparts and safe to non target organisms and safe to the environment".

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

Designation:	Corn NK 603 (Roundup Ready [®] Maize)
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:	Untransformed parental corn line LH82 x B73
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 (Glyphosate) tolerance
Trait Introduction Method:	Particle acceleration method

Donor Organism:	<i>Agrobacterium sp.</i> Strain CP4, source of <i>cp4epsps</i> gene which encodes only for the naturally glyphosate-tolerant EPSPS protein
Pathogenicity:	The <i>cp4</i> gene was derived from the common soil bacterium <i>Agrobacterium sp.</i> Strain CP4 which encodes only for the naturally glyphosate-tolerant EPSPS protein. No other protein is produced or introduced which may bring about toxicity, allergenicity or may be anti-nutritional in nature. Proven to be a safe source. No known pathogenicity in humans and animals because of the absence of the shikimic acid pathway in animals.
Proposed Use:	For direct use as food, feed and for processing and for propagation

II. Background Information

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.

Using the method of modern biotechnology, Monsanto Company has developed Roundup Ready® corn hybrids that confer tolerance to glyphosate, the active ingredient in Roundup® agricultural herbicides, by the production of 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) proteins that naturally confer tolerance to glyphosate. Glyphosate kills plants by inhibiting the enzyme EPSPS.

On May 6, 2003, Monsanto Philippines Inc. submitted an application to the Bureau of Plant Industry requesting for biosafety permit for direct use under AO#8 part 5 for corn event NK 603 which has been genetically modified for herbicide resistance. Similarly, on December 14, 2004, Monsanto Philippines, Inc. submitted an application for propagation for corn NK 603.

Monsanto Philippines, Inc. has provided data on the identity of corn NK 603, 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 NK 603 has been evaluated according to BPI's safety assessment by concerned agencies: [Bureau of Animal Industry (BAI), Bureau of Plant Industry (BPI), Bureau of Agriculture, Fisheries and Product Standards (BAFPS) and Fertilizer and Pesticide Authority (FPA)] 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 Public Information Sheet for application for direct use on two widely circulated newspapers (Malaya and Daily Tribune) on June 6, 2003 and published PIS for application for propagation on two widely circulated newspapers (Philippine Star and Manila Bulletin) on December 21, 2004 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 Event NK 603 (Trade name: Roundup-Ready Corn) and all corn lines/hybrids derived from this Event contain the CP4 EPSPS coding sequence from *Agrobacterium sp* CP4 strain. The CP4 EPSPS sequence encodes for the production of the naturally-occurring CP4 EPSPS protein that renders the corn NK 603 tolerant to glyphosate, a herbicide known to be environmentally-compatible. The EPSPS enzyme is present in the shikimic acid pathway for the biosynthesis of aromatic amino acids in plants and microorganisms. Inhibition of this enzyme by glyphosate leads to a deficiency in the

production of aromatic acids and lack 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 recommendations.

Safety of the Expressed Proteins

The potential toxicity effects of proteins are deduced by comparing the amino acid sequence of the introduced protein to known protein toxins. Bioinformatics assessments of CP4 EPSPS protein established that the protein is similar only to proteins of the EPSPS gene family, and are not similar to toxins or other pharmacologically active proteins contained in the PIR, EMBL, SwissProt, and GenBank protein sequence databases. Also, studies showed that there were no indications of toxicity in mice administered CP4 EPSPS protein by oral gavage.

Moreover, CP4 EPSPS proteins are not homologous to known protein allergens included in the available genetic databases (GenBank, EMBL, PIR, and SwissProt). Furthermore, these proteins are present at very low levels in Roundup Ready corn and are from a family of proteins with long history of safe consumption.

IV. Nutritional Composition (Compositional Analysis)

Under the same agronomic condition as conventional counterpart corn, the CP4 EPSPS does not alter the quantity and quality of the key components: proximate analysis, amino acids, fatty acids, Vitamin E and minerals, including phytic acid and trypsin inhibitors. It also does not alter the quantity and quality of the (secondary) metabolites, namely ferulic acid, p-coumaric acid and raffinose.

The nutritional equivalence of RR corn to conventional corn was confirmed in numerous feeding studies with broiler chickens and rats which included clinical and histological evaluations. The environmental impact of RR corn is also comparable to conventional corn.

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 event NK 603 fell within the range found in non-transgenic corn.

VI. Environmental Assessment

Wide adoption of transgenic corn (NK 603) in combination with glyphosate usage, will minimize tillage practices related to weed control (through land preparation, inter-row cultivation) and will rebound to better soil conservation. Weed control is total and far superior than selective herbicides like Atrazine. No adverse environmental impact is foreseen since voluminous accounts of studies worldwide attest to the safety of glyphosate to the ecosystems.

Glyphosate tolerance has no pleiotropic effect on pest and disease reaction except that if all weed hosts as food source are removed and since there is no protection (genetic) against insect pests, there is a likelihood that damage to corn can intensify.

The transgenic corn may cross-pollinate with non-transgenic corn varieties (and vice versa) but the acquired gene will not persist in natural populations because there is no selection pressure in favor of the gene (unlike in pest resistance). Gene flow is nil. No possibility

As has been indicated, Tigbi or *Coix lacryma* is the nearest relative of maize in the Philippines but incompatibility has set them apart even with human intervention. No mitigating measures required since corn is genetically isolated as far as Tigbi or wild relative are concerned.

The only means of dissemination of corn is through seeds and corn is not known to have become a weed any place else in the world. RRC NK603 is not likely to be a weed, since it does not possess weedy tendencies, and it is not included in the list of weeds in standard texts and references. The addition of the cp4 epsps gene is not expected to add any characteristics of weediness to NK603.

There are no observed difference in insect / arthropod fauna between RR corn and conventional corn.

The applicant submitted a report on the performance of glyphosate-tolerant corn (NK603) and its hybrid counterpart (normal) DK818 under field conditions in 9 locations in the dry season of 2003-2004 and 3 locations during the wet season in 2004. Two applications (on crop) of glyphosate at two corn leaf stages of tolerant NK603 showed complete control of all weeds. Yields were very high at more than 6 tons per hectare and the technology proved more economical than if repeated row-cultivation and hand weeding were performed. The advantage therefore was in minimizing tillage operations and affecting better soil conservation. Glyphosate residue analysis of soil, corn grain and stover indicated that glyphosate applications did not produce any detectable level, thus lending support to world-wide reports on safety from the ecological standpoint. Glyphosate breakdown (through microbial action) does not produce secondary metabolites that can accumulate in the soil, thus repeated application of the chemical season-after-season will not pose a risk.

VII. Regulatory Decision

After reviewing the scientific data and information relevant to the application of Monsanto Philippines Inc., it is concluded that corn 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 or feed or for processing and for propagation is as safe and substantially equivalent to its unmodified counterpart, safe to non target organisms or safe to the environment and is therefore approved for direct use as food, or feed or for processing and for propagation. Monsanto shall duly inform the public of the approval for direct use 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. The biosafety permit for propagation is subject to submission, approval and compliance to a post monitoring plan on the possible evolution of weeds developing resistance to glyphosate and a change in weed population. Changes in arthropod population (species and density) should also be monitored.