

FACT SHEET
APPLICATION FOR APPROVAL FOR RELEASE OF PRODUCTS OF
MIR604 CORN
FOR SUPPLY OR OFFER TO SUPPLY FOR SALE OR PLACING IN THE
MARKET

NBB REF NO: JBK(S) 602-1/1/22

The objective of the Biosafety Act is to protect human, plant and animal health, the environment and biological diversity. Under the Biosafety Act, the National Biosafety Board (NBB) is currently assessing an application for approval submitted by Syngenta Crop Protection Sdn. Bhd.

1. What is the application for?

This application is to import and release MIR604 corn (maize; *Zea mays* L.) and its products.

2. What is the purpose of the import and release?

The purpose of the import and release is to supply or offer for sale/ placing on the market of MIR604 corn for direct use as food and feed and for processing (FFP).

3. How has the MIR604 corn been modified?

Corn derived from insertion event MIR604 (marketed under the brand name Syngenta Agrisure™ RW) is genetically modified (GM) to produce a protein that controls corn rootworms (*Diabrotica spp.* [Coleoptera]). This protein, a modified Cry3A protein (mCry3A), is produced from the transgene *mcry3A*, a synthetic gene that is related to the native *cry3A* gene found in the naturally occurring soil bacterium *Bacillus thuringiensis (Bt)*. Additionally, a marker transgene, *pmi*, has been added to allow the selection of transformed plants during development. The gene *pmi* was isolated from the common bacteria *Escherichia coli*. The protein produced by this gene is the enzyme phosphomannose isomerase (PMI). MIR604 corn was produced by *Agrobacterium*-mediated transformation of a proprietary line of corn with the transformation plasmid vector pZM26.

4. Characteristics of MIR604 corn

(a) Details of the parent organism

The recipient or parental plant is *Zea mays* L. , also known as corn. Corn is one of the world's leading cereal crops, ranked after wheat and rice, and is grown in over 25 countries. Corn has a long history of safe use as food for consumption by humans and other animals. No significant native toxins are reported to be associated with the genus *Zea*. A major proportion of grain and forage derived from corn is used in animal feed. Corn-derived products are also routinely used in a large number and diverse range of foods for human consumption. Such products include flour, breakfast cereals, high fructose corn syrup and starch products.

Corn grain is also used to produce industrial products, such as ethanol by fermentation.

(b) Details of the donor organism

The native gene *cry3A* is derived from *B. thuringiensis* subsp. *tenebrionis*. Insecticidal Cry proteins from *B. thuringiensis* have a long history of safe use in food crops and microbial pesticide products. The transgene *mcry3A* in MIR604 corn is a modified *cry3A* gene to encode mCry3A protein for enhanced activity against target pests. Additionally, the gene was engineered to accommodate the preferred codon usage for corn.

The gene *pmi*, also known as *manA*, was derived from *E. coli* strain K-12, a non-pathogenic strain. *E. coli* is a normal inhabitant of the intestinal flora of humans and other animals, where it doesn't normally cause disease.

(c) Description of the trait(s) and characteristics which have been introduced or modified

MIR604 corn contains the transgenes *mcry3A* and *pmi*. MIR604 corn is insecticidally active against certain Coleoptera, including western corn rootworm (*Diabrotica virgifera virgifera*), northern corn rootworm (*D. longicornis barberi*), and Mexican corn rootworm (*D. virgifera zea*), which are significant pests of corn in the United States. Protection against coleopteran pests is provided through expression of mCry3A protein.

The amino acid sequence of the encoded mCry3A corresponds to that of the native Cry3A, except that its N-terminus corresponds to methionine 48 of the native protein and a cathepsin G protease recognition site has been introduced, beginning at amino acid residue 155 of the native protein. This modification increases the toxicity to target pests, particularly *D. virgifera virgifera* and *D. longicornis barberi*. The entire coding region of *mcry3A* was synthesized to accommodate the preferred codon usage for corn.

The *pmi* transgene, also known as *manA*, which encodes the enzyme phosphomannose isomerase, was utilized as a plant selectable marker during development of MIR604 corn. The PMI enzyme catalyzes the isomerization of mannose-6-phosphate to fructose-6-phosphate. It allows transformed corn cells to utilize mannose as a primary carbon source in culture media, whereas cells that lack *pmi* expression will fail to proliferate.

(d) Safety of the expressed protein

Cry proteins have been used in agriculture for many years and their safety has been well-established. Human safety has previously been established for a range of Bt crystal (Cry) proteins, and supports the prediction that no adverse health effects will result from exposure to the mCry3A protein present in MIR604 corn. The mCry3A protein is exempt from food and feed tolerances in corn in the USA (US Code of Federal Regulations 40

CFR §174.505), as are all other Cry proteins in commercial GM crops and microbial pesticides.

The safety of PMI has been established previously, and it is exempt from food and feed tolerances in all crops in the USA (US Code of Federal Regulations 40 CFR §174.527). Small amounts of PMI proteins from various sources have always been present in the food and feed supply as a result of the ubiquitous occurrence of PMI proteins in nature, including in food plants and animals. PMI proteins have been found in such diverse plant species as tobacco, walnut and *Brassica* species as well as in seeds of soybeans and other legumes.

5. Assessment of Risks to Human Health

Food and feed products derived from MIR604 corn are not materially different from food and feed products derived from conventional corn.

(a) Nutritional Data

MIR604 corn grain is compositionally equivalent to non-transgenic corn grain in terms of proximate composition, key nutrients, vitamins, minerals, and anti-nutrients. There are no biologically significant differences (including nutritional differences) between MIR604 corn and non-transgenic corn, with the exception of the intended traits conferred by expression of the mCry3A and PMI proteins, which have been demonstrated to be safe for food and feed uses.

(b) Toxicology

Both mCry3A and PMI were demonstrated to be non-toxic at high doses in acute oral toxicity tests in mammals. PMI is a non-toxic enzyme involved in sugar metabolism, and mCry3A protein is toxic only to the larvae of certain coleopteran (beetle) insect species. Other organisms, including mammals, lack the specific gut receptors necessary for mCry3A protein to exert its toxic action. Exposure to mCry3A and PMI proteins is expected to be minimal because very low concentrations are present in MIR604 corn and because both proteins are rapidly digested in simulated mammalian gastric and intestinal fluids. MIR604 corn grain was not toxic in animal feeding studies, and is compositionally equivalent to conventional corn grain.

(c) Allergenicity

Neither mCry3A nor PMI proteins is likely to be allergenic, based on their derivation from nonallergenic source organisms (bacteria), a lack of biologically relevant sequence similarity to known allergens, minimal exposure following rapid digestion, and lack of glycosylation (a characteristic observed in some allergens). Exposure to mCry3A and PMI proteins is expected to be negligible, because very low concentrations are present in MIR604 corn and because each protein is rapidly digested in simulated mammalian gastric and intestinal fluids.

6. Assessment of Risks to the Environment

The application does not cover an environmental release. The release is intended only to cover the import of the MIR604 corn products from countries where the maize is already approved and commercially grown, and that may enter Malaysia as food, feed and for further processing (FFP).

7. What is the Emergency Response Plan?

(a) First Aid Measures

No special first aid measures are required for exposure to this product.

(b) Accidental Release Measures

It is possible for seed to be accidentally released during transport, however, corn (*Zea mays*) is not weedy in character. Corn has lost the ability to survive without cultivation) and is very uncompetitive against perennial vegetation. The agronomic and phenotypic characteristics of MIR604 corn were compared to those of conventional corn. No differences indicative of increased weediness potential were observed in plant growth habit, vegetative vigor, flowering characteristics or yield.

Further, the environmental safety of the introduced mCry3A and PMI proteins in MIR604 corn has been established. With the exception of certain target *Diabrotica* beetle species, mCry3A has been demonstrated to be nontoxic to all test organisms. Exposure of nontarget invertebrates, mammals, birds and fish to mCry3A in laboratory and feeding studies at concentrations equal to or greater than estimated environmental concentrations via cultivation of MIR604 corn showed no adverse effects. Similarly, PMI was also shown to be nontoxic in relevant laboratory and feeding studies.

(c) Handling and Storage

There are no specific instructions or recommendations for use, storage and handling of MIR604 corn. The characteristics of MIR604 corn and products derived from it are not different from those of conventional corn, apart from the introduced traits. The same measures for handling and storage for conventional corn are valid for MIR604 corn.

(d) Disposal Considerations

MIR604 corn has been assessed as being as safe as its conventional non-GM corn counterpart. Waste grain and processed products from MIR604 corn may be disposed of and treated in the same way as grain and processed products of non-GM corn.

8. How can I comment on this application?

Any member of the public may submit their comments or queries on publicly notified information about the application. Before submission of

comments or queries, the person should review the information provided. Comments and queries on any possible impacts/risks to the health and safety of the people and the environment that may be posed by the proposed release are appreciated. The submission of comments or queries should be prepared carefully as it will be given the same scrutiny as the application by the NBB. The submission of comments and clarifications or queries should contribute to the NBB's assessment. Even if the submission is not science-based, and focuses on cultural or other values, it should still be developed in the form of a well-founded argument.

Please note that the consultation period closes on **30th October 2015** and written submissions

are required by that date. Submissions must be addressed to:

**Director General, Department of Biosafety
Ministry of Natural Resources and Environment
Level 1, Podium 2, Wisma Sumber Asli
No. 25, Periaran Perdana, Presinct 4, 62574
Putrajaya, MALAYSIA.
E-mail: biosafety@nre.gov.my.
Fax: 03-88904935.**

Please include your full name, address and contact details in your submission.

Reference

US Code of Federal Regulations 40 CFR §174.505

US Code of Federal Regulations 40 CFR §174.527