

**ASSESSORS' CONSOLIDATED REPORT ON MONSANTO PHILIPPINES INC.'
CORN MON 87427 x MON 89034 x MON 810 x MIR162 x MON87411 x MON 87419
APPLICATION FOR DIRECT USE AS FOOD AND FEED, OR FOR PROCESSING**

EXECUTIVE SUMMARY

On May 24, 2021, Monsanto Philippines Inc., filed for application of corn MON 87427 x MON 89034 x MON 810 x MIR162 x MON87411 x MON 87419 for direct use as food and feed, or for processing, as original application under the DOST-DA-DENR-DOH-DILG Joint Department Circular (JDC) No. 1 Series of 2016. After reviewing the Risk Assessment Report and attachments submitted by the applicant, the assessors namely: Scientific and Technical Review Panel (STRP), BPI Plant Products Safety Services Division (BPI-PPSSD) and Bureau of Animal Industry- Biotech Team (BAI-BT), concurred that corn MON 87427 x MON 89034 x MON 810 x MIR162 x MON87411 x MON 87419 is as safe for human food and animal feed as its conventional counterpart.

The Department of Environment and Natural Resources – Biosafety Committee (DENR-BC), after a thorough scientific review and evaluation of the documents related to Environmental Risk along with the submitted sworn statement and accountability of the proponent, recommended the issuance of a biosafety permit for this regulated event, provided that the conditions set by DENR are complied. Also, the Department of Health – Biosafety Committee (DOH-BC), after a thorough scientific review and evaluation of documents related to Environmental Health Impact, concluded that corn MON 87427 x MON 89034 x MON 810 x MIR162 x MON87411 x MON 87419 will not pose any significant risk to the health and environment and that any hazards could be managed by the measures set by the department. DOH-BC also recommended for the issuance of biosafety permit for the transformation event.

Furthermore, the Socio-economic, Ethical and Cultural (SEC) Considerations expert also recommended for the issuance of biosafety permit for this regulated article after assessing the socio-economic, social and ethical indicators for the adoption of Genetically Modified Organisms.

Background

In accordance with Article VII. Section 20 of the JDC, no regulated article, whether imported or developed domestically, shall be permitted for direct use as food and feed, or for processing, unless: (1) the Biosafety Permit for Direct Use has been issued by the BPI; (2) in the case of imported regulated article, the regulated article has been authorized for commercial distribution as food and feed in the country of origin; and (3) regardless of the intended use, the regulated article does not pose greater risks to biodiversity, human and animal health than its conventional counterpart.

The BPI Biotech Office provided the assessors the complete dossier submitted by Monsanto Philippines Inc. The SEC expert, on the other hand, was provided with a questionnaire on socio-economic, ethical and cultural considerations that have been addressed by corn MON 87427 x MON 89034 x MON 810 x MIR162 x MON87411 x MON

87419 in relation to their application. These assessors were given thirty (30) days to submit their independent assessment to BPI Biotech Secretariat.

INFORMATION ON THE APPLIED EVENTS

Monsanto Company has used conventional breeding techniques to develop MON 87427 × MON 89034 × MON 810 × MIR162 × MON 87411 × MON 87419, a combined trait maize product that confers herbicide tolerance and insect resistance. This combined trait maize product also contains a trait that causes glyphosate-induced, non-viable pollen in inbred lines, which facilitates the production of hybrid seed.

MON 87427 utilizes a specific promoter and intron combination to drive CP4 EPSPS protein expression in vegetative and female reproductive tissue. Little to no CP4 EPSPS protein is expected to be produced in MON 87427 pollen, thus providing maize lines with tissue-selective glyphosate tolerance to facilitate the production of viable hybrid maize seed.

MON 89034 produces two insecticidal proteins that protect against feeding damage caused by specific lepidopteran insects such as the European corn borer (ECB; *Ostrinia nubilalis*), Asian corn borer (ACB; *Ostrinia funicularis*), corn earworm (CEW; *Helicoverpa zea*), fall armyworm (FAW; *Spodoptera frugiperda*), and common cutworm (CW; *Spodoptera litura*). Cry1A.105 is a modified *Bacillus thuringiensis* (*Bt*) Cry1A protein and Cry2Ab2 is a *Bt* (subsp. *kurstaki*) protein. The combination of the two insecticidal proteins provides enhanced insect control and offers an additional insect resistance management tool.

MON 810 produces the Cry1Ab insecticidal crystal (*Cry*) protein (δ -endotoxin) derived from *Bt* subsp. *kurstaki* (*B.t.k.*). The Cry1Ab protein provides protection from feeding damage caused by ECB (*Ostrinia nubilalis*).

MIR162 produces the *Bt* Vip3Aa20 protein, which protects against feeding damage caused by lepidopteran insect pests like CEW (*Helicoverpa zea*). MIR162 also expresses the phosphomannose isomerase (PMI) enzyme from *Escherichia coli*, as a plant selectable marker.

MON 87411 confers protection against corn rootworm (CRW; *Diabrotica spp.*) and tolerance to the herbicide glyphosate. MON 87411 contains a suppression cassette that expresses an inverted repeat sequence designed to match the sequence of western corn rootworm (WCR; *Diabrotica virgifera virgifera*). The expression of the suppression cassette results in the formation of a double-stranded RNA (dsRNA) transcript containing a 240 bp fragment of the WCR *Snf7* gene (DvSnf7). Upon consumption, the plant produced dsRNA in MON 87411 is recognized by the CRW's RNA interference (RNAi) machinery resulting in downregulation of the targeted DvSnf7 gene leading to CRW mortality. MON 87411 also contains a *cry3Bb1* gene that produces a modified *Bt* (subsp. *kumamotoensis*) Cry3Bb1 protein to protect against CRW larval feeding. In addition, MON 87411 contains the *cp4 epsps* gene from *Agrobacterium sp.* strain CP4 that encodes for the 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) protein, which confers tolerance to glyphosate, the active ingredient in Roundup® agricultural herbicides.

MON 87419 is tolerant to the herbicides dicamba (3, 6-dichloro-2-methoxybenzoic acid) and glufosinate (2-amino-4-(hydroxymethylphosphinyl) butanoic acid). MON 87419 contains a demethylase gene from *Stenotrophomonas maltophilia* that expresses a dicamba mono-oxygenase (DMO) protein to confer tolerance to dicamba herbicide and the phosphinothricin N-acetyltransferase (*pat*) gene from *Streptomyces viridochromogenes* that expresses the PAT protein to confer tolerance to glufosinate-ammonium, the active ingredient in Liberty® herbicide.

MON 87427, MON 89034, MON 810, MIR162, MON 87411, and MON 87419 were independently approved in the Philippines for direct use as food and feed, or for processing by the DA – BPI: MON 87427 (April, 2021*), MON 89034 (September, 2019*), MON 810 (February, 2018*), MIR162 (October, 2018*), MON 87411 (November, 2018) and MON 87419 (August, 2019).

Countries Where Approvals Have Been Granted

Country	Food	Feed
	direct use or processing	direct use or processing
Japan	2018	2018

Source: <https://www.isaaa.org/gmapprovaldatabase/event/default.asp?EventID=547>

STRP'S ASSESSMENT

1. Gene Interaction

The safety of the individual products and the proteins derived from the products have been thoroughly assessed by molecular characterization, compositional and nutritional equivalency, toxicity studies and environmental assessment. Based on the data generated from these studies, there is no likelihood of potential interaction among the proteins. The proteins are likely to accumulate in the chloroplast and cytoplasm of maize cells. Further, there is yet no elucidated mechanism to describe this interaction to produce a new allergen or a new toxin. [1][6][7].

2. Metabolic Pathways

The CP4 EPSPS, Cry1A.105, Cry2Ab2, Cry1Ab, Vip3Aa20, PMI, Cry3Bb1, DMO, and PAT (pat) proteins and DvSnf7 RNA have different modes of actions as described in the report by Monsanto Philippines, Inc. dated May 2021.[10].

3. Gene Expression

- a. Each individual protein products (CP4 EPSPS, Cry1A.105, Cry2Ab2, Cry1Ab, Vip3Aa20, PMI, Cry3Bb1, DMO, and PAT (pat) proteins) were expressed in the combined trait product: MON 87427 × MON 89034 × MON 810 × MIR162 × MON 87411 × MON 87419.[1].
- b. Protein levels for MON 87427, MON 89034, MON 810, MIR162, MON 87411 and MON 87419 are low. This has been assessed separately based on the previous reports of BPI-BIOTECH. Further, the levels of proteins in each of the single events are similar to the combined trait product.[1].
- c. There are no possibilities of interaction which may affect the stability and expression levels of each gene.[1].

STRP's Conclusion

After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines, Inc. relevant to combined trait maize MON 87427 × MON 89034 × MON 810 × MIR162 × MON 87411 × MON 87419, the STRP found scientific evidence that the regulated article applied for direct use has no evidence of interaction on the resulting gene products. This product was developed through conventional plant breeding techniques from the single event products, MON 87427, MON 89034, MON 810, MIR162, MON 87411, and MON 87419.

BAI'S Assessment

1. Gene Interaction

- a. Due to the differences in the mechanism of the genes inserted, the gene products of the stacked transgenic corn (MON 87427 × MON 89034 × MON 810 × MIR162 × MON 87411 × MON 87419) are highly unlikely to create an interaction that will lead to the generation of a potential toxin or allergen.[1][2][3][4][5].
- b. The proteins Cry2Ab2, DMO, and CP4 EPSPS will be accumulated in the chloroplast of the plant cells in which they contain the site-specific promoter in their expression cassettes from their respective single events. On the one hand, the remaining proteins PAT, Cry1a.105, PMI, Vip3Aa20, Cry1Ab, Cry3Bb1 will only be expressed in the cytoplasm of the maize cells since they do not have such promoters that will specify the location of its expression.[1][8][9].

2. Metabolic Pathways

a. Each gene product was completely described in the attached references of this application and in the previous single transformation events. [1][8][9].

b. Each protein has its own mode of action as enumerated below:

- Cry proteins (Cry1A.105, Cry1Ab, Cry2Ab2, and Cry3bb1) – proteins derived from *Bacillus thuringiensis* genes which confer to insecticidal properties specific to lepidopterans and coleopterans
- Phosphomannose isomerase (PMI) – a marker which converts mannose-6-phosphate to fructose-6-phosphate, allowing the transgenic plant to survive in a selective culture media
- CP4 EPSPS – confers to herbicide-tolerance in which the protein 3-phosphoshikimate 1-carboxyvinyltransferase reduces the affinity of the plant to glyphosate
- PAT – selective marker for acetylation of phosphonitrilic acid, making the plant tolerant to glufosinate-ammonium herbicides
- Vip3Aa20 – lepidopteran-resistance of the plant
- DMO – demethylation of the dicamba herbicide (herbicide tolerance)
- DvSnf7 suppression cassette -produces dsRNA transcript that alters the DvSnf7 mRNA machinery of the Western Corn Rootworm, rendering it to be fatal to the insect.

[1][11][12][13][14][15][16][17][18].

3. Gene Expression

a. The expression levels of the gene products from the stacked event are comparable to the individually approved single transformation events.[1][8][9].

b. The values are comparable as presented in tabular form and in the attached appendices of this application. Approved relevant consolidation reports were also cited for this evaluation.[1][8][9].

c. Interaction of the transgenes is not possible and thereby will not affect the expression levels of the gene products. In addition, each gene product has its own mode of action.[1][3][4][19].

BAI's Conclusion

After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines Inc. relevant to combined trait maize MON 87427 × MON 89034 × MON 810 × MIR162 × MON 87411 × MON 87419, the BAI found scientific evidence that the regulated article applied for direct use has no evidence of interaction on the resulting gene products.

BPI-PPSSD'S Assessment

1. Gene Interaction

- a. No interaction is expected on the resulting product, since safety conclusion of single events can be applicable to the safety of combined trait product produced by conventional breeding of two or more single events.[28]
- b. Any likelihood of interaction will not likely lead to production of a new allergen or toxin in the combined trait product, since the modes of action are very different for the CP4 EPSPS, Cry1A.105, Cry2Ab2, Cry1Ab, Vip3Aa20, PMI, Cry3Bb1, DMO, and PAT (*pat*) proteins, and DvSnf7 RNA, suggesting that the proteins and RNA act independently. The likelihood of potential interaction with one another is not considered to be significant that could affect the stability and expression level of each gene nor lead to production of a new allergen or toxin in the combined trait product. Furthermore, there is no known mechanism of interaction among the proteins that could lead to adverse effects in humans, animals or environment. [28]
- c. Given that the modes of action of each introduced gene are different from each other, each trait or protein will function independently as in single events. Therefore, it is unlikely that there are unintended adverse effects from inserted traits by combining them through conventional breeding. [28].

2. Metabolic Pathways

- a. CP4 EPSPS proteins are involved in the biochemical shikimic pathway producing aromatic amino acid in the chloroplasts. It catalyzes the transfer of enolpyruvyl group from phosphoenol pyruvate (PEP) to the 5-hydroxyl of shikimate-3-phosphate (S3P) producing inorganic phosphate and 5-enolpyruvylshikimate-3-phosphate. This mechanism is being inhibited with glyphosate binding which blocks the binding of EPSPS to PEP. CP4 EPSPS, on the other hand, has higher affinity for PEP thus allowing the catalysis. This enzyme catalyzes the reaction wherein the enolpyruvyl group from phosphoenol pyruvate (PEP) is transferred to the 5-hydroxyl of shikimate-3-phosphate (S3P) to form 5-enolpyruvylshikimate-3-phosphate (EPSPS) and inorganic phosphate (Pi).[1][21][22][23][24][25][30].
- b. Hofte and Whiteley (1989) had described the mode of actions of insecticidal crystal (Cry) proteins of *Bacillus thuringiensis*. Cry proteins have been divided into four (4) major classes and several subclasses characterized by both structural similarities and insecticidal spectra of the encoded proteins. Different classes and subclasses of Cry proteins bind selectively to specific sites in the midgut cells of susceptible insect species. The binding leads to the formation of cation-specific

pores that disrupt the midgut ion flow, swelling of cells due to an influx of water, cell lysis, paralysis and death of insect. Cry1 proteins including Cry1Ac are specific to lepidopterans.[1][21][22][23][24][25][30].

- c. Another protein that is toxic to lepidopteran insects is the Vip3Aa20. It has a different structural composition in contrast to its Cry protein counterparts, although Vip3Aa20 still has an equivalent toxicity towards lepidopteran species. It confers its mode of action by secretion into the extracellular environment, with its expressions manifested in the stationary phase, which is also a period of sporulation.[1][21][22][23][24][25][30].
- d. PMI enzyme catalyzes the reversible conversion of mannose 6-phosphate and fructose 6-phosphate and enables many microorganisms to utilize mannose as a carbon and energy source. Transformed plant cells with *pmi* gene are able to survive and grow on mannose-containing selective media.[1][21][22][23][24][25][30].
- e. DMO catalyzes the demethylation of dicamba to the non-herbicidal compound. DMO forms three component system comprised of a reductase, a ferredoxin, and a terminal oxygenase which functions together in a redox system, to transport electrons from nicotinamide adenine dinucleotide (NADH) to oxygen and catalyze the demethylation of dicamba.[1][21][22][23][24][25][30].
- f. The gene product CP4 EPSPS in MON 87427; Cry1A.105, Cry2Ab2 in MON 89034; Cry1Ab in MON 810; Vip3Aa20 and PMI in MIR162; Cry3Bb1, CP4 EPSPS and DvSnf7 dsRNA in MON 87411; DMO, and PAT in MON 87419 have different modes of action and did not cause any interaction based on the protein expression.[1][21][22][23][24][25][30].

3. Gene Expression

Validated multiplexed immunoassays and enzyme linked immunosorbent assays (ELISAs) for protein expression were used to assess the levels of CP4 EPSPS, Cry1A.105, Cry2Ab2, Cry1Ab, Vip3Aa20, PMI, Cry3Bb1, DMO, and PAT (*pat*) proteins in tissues of the combined trait product MON 87427 × MON 89034 × MON 810 × MIR162 × MON 87411 × MON 87419, and the singles MON 87427, MON 89034, MON 810, MIR162, MON 87411, and MON 87419. The CP4 EPSPS, Cry1A.105, Cry2Ab2, Cry1Ab, Vip3Aa20, PMI, Cry3Bb1, DMO and PAT (*pat*) proteins expression levels in the combined trait product MON 87427 x MON 89034 x MON 810 x MIR62 x MON 87411 x MON 87419 is same as to its corresponding single events.[23].

BPI-PPSSD'S Conclusion

After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines Inc. relevant to combined trait maize MON 87427 × MON 89034 × MON 810 × MIR162 × MON 87411 × MON 87419, and the history of approval of each single event, the PPSSD found scientific evidence that the regulated article applied for direct use has no evidence of interaction on the resulting gene products that is likely to produce new allergen or toxin. The nutritional data demonstrates that product MON 87427 × MON 89034 × MON 810 × MIR162 × MON 87411 × MON 87419 is substantially equivalent to the conventional counterpart.

DENR-BC'S Assessment

After a comprehensive review and evaluation of the documents and scientific evidence from literature submitted by Monsanto Philippines, Inc. concerning its application for direct use as food and feed, or for processing (FFP) of corn MON 87427 × MON 89034 × MON 810 × MIR162 × MON 87411 × MON 87419 (stacked traits), the DENR-BC considered that the regulated article poses no significant adverse effect to the environment and non-target organisms on the following bases:

1. It is less likely that the regulated article would persist in the environment in case of unintended release. Corn does not grow in unmanaged or uncultivated habitats;
2. Corn has a history of safe use, the regulated article is substantially equivalent to its conventional counterpart, and the stacked event is developed through conventional breeding methods and techniques. The chance that the regulated article becomes invasive or produces a weedy type of corn is remotely likely;
3. The introduced gene products are not harmful if ingested by non-target organisms and other wildlife, since the gene products conferring herbicide tolerance has no similarity to any known toxin, and the endotoxin derived from the *cry* genes in *Bacillus thuringiensis* is only harmful to its target insect pests;

[39][40][41].

DENR-BC'S Conclusion

After a thorough review and evaluation of the documents provided by the proponent Monsanto Philippines, Inc, through the Bureau of Plant Industry (BPI), in support of their application for approval for direct use as food, feed or for processing (FFP) of corn MON 87427 x MON 89034 x MON 810 x MIR162 x MON 87411 x MON 87419, the DENR-BC considered the regulated article safe to the environment, particularly on biodiversity.

DOH-BC's Assessment

After a thorough review and evaluation of the documents provided by the proponent Monsanto Philippines, Inc, through the Bureau of Plant Industry (BPI), in support of their application for approval for direct use as food, feed or for processing (FFP) of corn MON 87427 x MON 89034 x MON 810 x MIR162 x MON 87411 x MON 87419, the following are the observations and recommendations:

1. Scientific pieces of evidence from toxicity studies and references, find that the regulated article will not cause significant adverse health effects to human health.
2. Dietary exposure to the regulated article is unlikely to result in allergic reaction.
3. The regulated article is as safe as food or feed derived from conventional corn varieties.
4. The regulated article is not materially different in nutritional composition from that of the non-transgenic corn or the conventional corn.

DOH-BC's Conclusion

The DOH-BC found that the regulated article applied for direct use as food, feed or for processing (FFP) is safe as its conventional counterpart and shall not pose any significant risk to human health.

SEC Expert's Assessment

- a. GM maize is widely produced and consumed and is a significant component of global trade of agricultural commodities. Based on the latest agricultural commodity data by the Philippine Statistics Authority (PSA), the volume of maize imports at 0.81 million metric tons grew by 13.15 percent. Its import payment was up by 7.33 percent and reached US\$ 212.21 million, accounting for 1.70 percent in the country's import value of agricultural products.
- b. In 2016, maize production in the country registered output losses of 3.99%. However, hog and dairy production grew by 5.25% and 3.78%, respectively. Importation therefore of maize as feed material has become more important to meet domestic demands. A six-year data suggests increasing value of maize imports in meeting the domestic needs for maize. The data however do not delineate maize imports dependency for feed production and propagation. [31][32][33][34][35][36].
- c. The availability of yellow maize as feeds material is vital to the competitiveness of the Philippines livestock and poultry sector. The "Philippine Agriculture: 2020" reports that the country is projected to have deficits of 683,000 metric tons of pork, 308,400 metric tons of broiler and 30,000 metric tons of eggs by 2020. Among other things, maize MON 87427 and the rest of the approved GM maize hybrids in the country can

aid reduce projected deficit and minimize imports, both in livestock produce and feed materials when imported in the country for direct use as food, feed or for processing. [31][37].

SEC Expert's Recommendation

After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines, Inc., relevant to corn MON 87427 x MON 89034 x MON 810 x MIR162 x MON87411 x MON 87419, the SEC expert recommended for the approval and issuance of biosafety permit of the said GM product.

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