

# **CONSOLIDATED REPORT ON SYNGENTA'S APPLICATION FOR DIRECT USE AS FOOD AND FEED, OR FOR PROCESSING OF COMBINED TRAIT PRODUCT CORN *Bt11 x MIR162 x MIR604 x TC1507 x 5307 x GA21***

## **EXECUTIVE SUMMARY**

On August 10, 2017, Syngenta Philippines Inc. applied the stacked trait product corn *Bt11 x MIR162 x MIR604 x MON89034 x 5307 x GA21* for direct use as food and feed, or for processing as an original application under the DOST-DA-DENR-DOH-DILG Joint Department Circular No. 1 Series of 2016 (JDC No.1, S2016).

After reviewing the Risk Assessment Report and attachments submitted by the applicant; the Scientific and Technical Review Panel (STRP) member, BPI-Plant Products Safety Services Division (BPI-PPSSD) and Bureau of Animal Industry (BAI) has found no interaction of the resulting gene product of the regulated article applied for direct use as food and feed, or processing based on scientific evidences provided.

The STRP, BAI, and BPI-PPSSD concurred that the likelihood of interaction of the proteins involved in the combined trait product: *Cry1Ab, Vip3Aa20, mCry3A, cry1A.105 and cry2Ab, eCry3.1Ab, mEPSPS, PAT and PMI*, is highly unlikely to produce any known allergen or toxins to human and animals because of the difference on their mode of action. There is no known mechanism of interaction among the RNA-based suppression and the proteins that could lead to adverse effects in human, animals or environment which is not likely to interact. Furthermore, the assessors affirmed that there are no possible unintended effects of stacked genes on the metabolism of the plant based on the previous assessments of individual transformation events. In addition, stability and expression of the gene will never be affected since molecular analyses also indicated the absence of any marker gene in *Bt11 x MIR162 x MIR604 x MON89034 x 5307 x GA21* genome.

After thorough scientific review and evaluation of Syngenta's duly accomplished Environmental Risk Assessment (ERA) and Project Description Report (PDR) forms, the Department of Environment and Natural Resources – Biosafety Committee (DENR-BC), recommended for 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 the accomplished Environmental Health Risk Assessment form, concluded that corn *Bt11 x MIR162 x MIR604 x MON89034 x 5307 x GA21* 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. Hence, the DOH-BC also recommended for the issuance of biosafety permit for the stacked trait product.

Lastly, after assessing that there will be no negative socio-economic, ethical and cultural concerns that will arise from the adoption of Genetically Modified Organisms, the Socio-economic, Ethical and Cultural (SEC) expert recommended for the approval and issuance of biosafety permit of corn *Bt11 x MIR162 x MIR604 x MON89034 x 5307 x GA21* for direct use as food and feed, or for processing.

## **BACKGROUND**

In accordance with Article VIII, Section 20 of the JDC No.1, S2016, 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, except for the SEC expert, the complete dossier submitted by Syngenta Philippines. The SEC expert, on the other hand, was provided with a separate questionnaire on socio-economic, ethical and cultural considerations that have been addressed by Syngenta Philippines in relation to their application.

Upon receipt of the individual reports from the assessors, the BPI Biotech staff prepared this consolidated risk assessment report for the information of the public.

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## **STRP, PPSSD, and BAI ASSESSMENT**

Bt11 x MIR162 x MIR604 x MON 89034 x 5307 x GA21 is a corn combined trait product developed by Syngenta Philippines, Inc. via conventional breeding techniques from the single event products Bt11, MIR162, MIR604, MON 89034, 5307 and GA21.

The single event Bt11 contains cry1Ab gene expressing Cry1Ab protein which confers resistance against certain lepidopteran insects and pat gene expressing PAT protein which confers tolerance to glufosinate ammonium herbicides. The event was approved by the Bureau of Plant Industry (BPI) for direct use as food and feed (FFP), or for processing on July 09, 2013.

MIR162 is another single event which contains vip3Aa20 gene encoding Vip3Aa20 which are proteolytically processed into active fragments which bind to specific receptors in the midgut epithelium of susceptible insects conferring protection against certain lepidopteran insects. The event also contains pmi gene expressing PMI protein which catalyzes the isomerization of mannose-6-phosphate into fructose-6-phosphate. The event was approved by BPI for FFP on February 11, 2015.

MIR604 and 5307 also contains PMI protein. Aside from this, MIR604 also contains mcry3A gene encoding mCry3A protein which confers resistance against certain Coleopteran insects such as corn rootworm. The event was approved by BPI for FFP on March 06, 2018 .

The event 5307 also contains ecry3.1Ab gene encoding eCry3.1Ab protein which confers resistance against certain Coleopteran insects. The event was approved by BPI for FFP on June 11, 2015.

MON 89034 contains cry1A.105 and cry2Ab2 genes encoding Cry1A.105 and Cry2Ab2 proteins, respectively. Both proteins confers resistance specifically against certain lepidopteran insects. The event was approved by BPI for FFP on April 29, 2014.

GA21 contains mepsps gene expressing mEPSPS protein which confers tolerance to glyphosate herbicides. The event was approved by BPI for FFP on November 23, 2013.

### *Gene Interaction*

Bt11 x MIR162 x MIR604 x MON 89034 x 5307 x GA21 contains expresses Cry1Ab, Vip3Aa20, mCry3A, Cry1A.105, Cry2Ab2 eCry3.1Ab, mEPSPS, PAT and PMI proteins which are not likely to interact due to their distinct mode of actions (Hofte and Whiteley, 1989; Lee et al., 2003; Kishore and Shah, 1988, De Block et al., 1987; Negrotto et al., 2000). The gene products will accumulate in different subcellular compartments of the plant parts (Herrero, 2017). Among the novel proteins only the Cry2Ab2 and mEPSPS are directed to the chloroplast since both are being regulated by a chloroplast transit peptide (CTP). The other proteins will accumulate in the cytoplasm as no cellular localization sequences are incorporated in the gene cassettes.

### *Metabolic Pathways*

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 Cry1Ab (a delta endotoxin) and Cry1A.105 are specific to lepidopterans. Cry2Ab2 targets lepidopteran insects too. However, heterologous-competition assays indicated a common binding site for toxins belonging to the Cry2A family that is not shared by Cry1A proteins. This indicates a different mode of action for Cry1 and Cry2 proteins. Cry3 proteins including mCry3A and eCry3.1Ab are specific to coleopterans such as corn rootworm.

Vip3Aa20 are proteolytically processed into active fragments which bind to specific receptors in the midgut epithelium of susceptible insects. Lee et al (2003) indicated that Vip and Cry proteins bind to different receptors through competitive binding assays.

The mEPSPS is involved in the shikimic pathway of aromatic amino acids in plants and microorganisms (Alibhai and Stallings, 2001; Kishore and Shah, 1988). It catalyzes the reaction where in the phosphoenol pyruvate (PEP) is transferred to 5-hydroxyl of shikimate-3-phosphate (S3P) to form 5-enolpyruvylshikimate-3-phosphate (EPSP) and inorganic phosphate (Pi).

Phosphinothricin N-acetyl transferase (PAT) detoxifies glufosinate ammonium through acetylation of phosphinothricin forming N-acetyl-glufosinate (NAG), 3-methylphosphinopropionic acid (MPP) and 3-methylphosphinicoacetic acid (MPA) (De Block, 1987). Phosphomannose isomerase (PMI) is involved in the isomerization of mannose-6-phosphate to fructose-6-phosphate (Negrotto et al, 2000).

Based from these pieces of information, each gene products are involved in different metabolic pathways based on the documents provided by the developer. Cry proteins and Vip3Aa20

protein have no enzymatic activities and are not involved in any metabolic pathways in plant metabolism (Hofte and Whiteley, 1989). PAT and PMI protein has an enzymatic activity. However, no endogenous substrate for the PAT has been identified in the maize plant except when PMI in corn is exposed to mannose (De Block et al, 1987; Negrotto et al, 2000). The modified EPSPS enzyme is involved in the shikimic pathway of the aromatic amino acids (Alibhai and Stallings, 2001; Kishore and Shah, 1988).

#### *Gene Expression*

The expression level of each novel proteins in different plant parts of Bt11 x MIR162 x MIR604 x MON 89034 x 5307 x GA21 was determined through Enzyme-linked Immunosorbent Assay (ELISA). Fifteen significant differences in the expression levels of the individual proteins in different plant parts were observed out of 67 statistical comparison between the stacked genes and the corresponding single events. Most of the differences were observed in kernels (reproductive stage and senescence stage). The concentration of PMI in the stacked hybrid was higher than in the corresponding single events, MIR162, MIR604 and 5307. Such difference can be attribute to the presence of three copies of pmi gene in the stack hybrid while the corresponding single events contains only one copy of the gene.

Based on the Southern blot analysis, the DNA hybridization patterns of the stacked corn hybrid corresponded to the hybridization bands observed for the single events indicating that the transgenic inserts from each single events were stably integrated in the stacked corn hybrid during the conventional breeding. However, the comparison of protein concentrations identified 15 significant differences in the expression levels of the individual proteins in different plant parts out of 67 statistical comparison between the stacked genes and the corresponding single events. Most of the differences were observed in kernels.

#### *Conclusion*

After a thorough and scientific evaluation of the documents provided by Syngenta Philippines, Inc. and other related literatures, scientific evidence indicates that the Combined Trait Product, Bt11 x MIR162 x MIR604 x MON 89034 x 5307 x GA21 applied for direct use as food and feed or for processing has no evidence of interaction on the resulting gene products and as safe as it's conventional counterpart.

#### **DENR-BC ASSESSMENT**

After a thorough and scientific review and evaluation of the documents provided by the Bureau of Plant Industry (BPI) on the application of Syngenta Philippines, Inc. for Direct Us as Food and Feed or for Processing of Corn Bt11 x MIR162 x MIR604 x MON89034 x 5307 x GA21, here under are the observations and appropriate and appropriate actions:

1. From the evaluation of the application submitted by the proponent, including the scientific evidences from provided references and literature, as well as other related studies, the Committee finds that the direct use of the regulated article whether for food, feed or for processing will not cause any significant adverse effect on the environment (land, air and water) and non-target organisms, to wit:
  - a) Genetic stability in the transgenic crop is ensured such that no unintended horizontal gene transfer shall occur to unrelated species.

- b) The protein product produced by the transgenic crop will degrade upon exposure to the natural environment and general conditions (i.e. high temperatures (60 °C and above), varying pH, enzyme digestion, etc.); and
- c) The protein product will not increase the weediness potential of the transgenic crop.

The evaluated support the conclusion that the regulated article is as safe as its conventional counterpart.

2. The project description report (PDR) discusses the specified environmental management plan indicating the possible risk and harm to the environment and non-target organisms as well as the mitigating measures and contingency plan of the proponent. Upon evaluation of the submitted PDR and environmental risk assessment (ERA), the Committee notes that the chances of unintended release or planting of the regulated article is very minimal and will not cause any damaging and lasting effects because the receiving environment (areas near the port, roads, railways, etc.) is not conducive for plant growth/germination.
3. The Bureau of Plant Industry (BPI) shall ensure the proper and secure packaging of the regulated article for transport and the safety and durability of the transport vehicle, for prevention of any possible spillage or unintended release during transport/import as per BPI's inspection in the port area.

The DENR-BC finds scientific evidence that the regulated article applied for Direct Use as food and feed or for processing is safe as its conventional counterpart and is not expected to pose any significant risk to the environment and to non-target organisms.

#### **DOH-BC ASSESSMENT**

After a thorough review and evaluation of the documents provided by the proponent, Syngenta 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 Bt11 x MIR162 x MIR604 x MON 89034 x 5307 x GA21. We, find that the regulated article applied for direct use as food and feed or for processing is as safe as its conventional counterpart and shall not pose any significant risk to human and animal health and environment.

The following are the observations and recommendations:

1. Scientific pieces of evidences from Toxicity studies and references, find that the regulated article will not cause significant adverse health effects to human and animal health.
2. Dietary exposure to the regulated article is unlikely to result allergic reaction.
3. The regulated article is as safe as food, feed derived from conventional corn varieties.
4. The regulated article is not materially different in nutritional composition from that of non-transgenic corn or the conventional corn.
5. It is suggested that the BPI ensure the following that clear labelling of the regulated article from the sources down to all levels of marketing stating that it is only for the purpose of direct use as food, feed or processing and is not to be used as planting materials.

Based on the above considerations and with submitted sworn statement and accountability of the proponent, this recommendation is being submitted to BPI related to the processing and issuance of the Biosafety Permit for Direct Use as Food , Feed or for Processing of Corn Bt11 x MIR162 x MIR604 x MON 89034 x 5307 x GA21.

## **SEC EXPERT EVALUATION**

The SEC expert agreed to the claim of the applicant that the importation of stacked corn Bt11 x MIR162 x MIR604 x MON89034 x 5307 x GA21, as raw materials for the food and feed industry, will help meet the local requirements while maintaining the trade between Philippines and US and other trade partners. Likewise, the SEC expert recommended for the approval of the GM application for Direct Use.

Though the GM application for direct use has been approved, it has been recommended that the seed company conduct or commission (in the future) research on the socio-cultural impacts of the said GM. Doing so would provide more concrete or empirical data to support the applicant's assertions when answering the questions on socio-economic, ethical, and cultural (SEC) considerations.