

**ASSESSORS' CONSOLIDATED REPORT ON MONSANTO PHILIPPINES INC'S COTTON  
MON15985 X MON1445 APPLICATION FOR DIRECT USE AS FOOD, FEED OR FOR  
PROCESSING**

**EXECUTIVE SUMMARY**

On December 13, 2019, Monsanto Philippines Inc. filed for application of cotton MON15985 X MON1445 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 Monsanto Philippines Inc., 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 cotton MON15985 X MON1445 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 cotton MON15985 X MON1445, 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 cotton MON15985 X MON1445 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 cotton MON15985 X MON1445.

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 cotton MON15985 X MON1445 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 EVENT

### Countries Where Approvals Have Been Granted (for FFP; for Commercial Propagation)

<b>Country</b>	<b>Food direct use or processing</b>	<b>Feed direct use or processing</b>	<b>Cultivation domestic or non- domestic use</b>
Australia			2002
Canada	2014	2014	
Costa Rica			2009
European Union	2002	2002	
Japan	2003	2003	
Mexico	2006		
New Zealand	2002		
Philippines	2004	2004	
South Korea	2004	2008	

Source: <https://www.isaaa.org/gmapprovaldatabase/event/default.asp?EventID=60> (Last updated: March 11, 2015)

## **STRP'S ASSESSMENT**

### **1. Gene Interaction**

- a. The insecticidal proteins Cry1AC, Cry2AB2 from MON15985 and the herbicide-tolerance proteins CP4 EPSPS from MON1445 and selectable marker proteins expressed in Corn MON 15985 × MON 1445 do not act on any similar metabolic pathway(s) nor share any intermediate metabolites in the biochemical or physiological pathways that the proteins act on or interfere with. The NPTII, and GUS proteins are primarily used as selectable marker, although expressed in the stacked event, did not indeed affect expression of the desired traits. There is no expected adverse effect on the target traits that the transgenes confer, more so, no new allergen nor toxin will be produced.[1].
- b. The resulting novel proteins of the stacked event will accumulate in different subcellular compartments of the plant. CP4 EPSPS and Cry2AB2 proteins will accumulate in the chloroplast while Cry1AC, GUS and NPTII proteins will be expressed in the cytoplasm.[1].

### **2. Metabolic Pathways**

- a. Cry2AB2 and Cry1AC are insecticidal proteins, CP4 EPSPS is a herbicide-tolerance protein, while GUS and NPTII are selectable markers - thus proving the claim that these novel proteins do not act on entirely the same physiological, metabolic, and biochemical pathways and do not share any intermediate metabolites in the pathways that they act on or interfere with. These proteins also have affinities and specificity to their respective substrates. Without the lack of interaction and very high substrate affinity, there is no expected adverse effect on the target trait that the transgenes confer, more so, no new allergen nor toxin will be produced.[1].
- b. There are no unintended nor unexpected effects on the metabolism of the cotton plant when the novel genes are introduced in it. The presented data depicts that the various agronomic characteristics of the stacked trait plant is statistically significantly different when compared to the conventional untransformed counterpart, although the values obtained are well within the range of accepted values from that of reference varieties of cotton.[1].

### **3. Gene Expression**

- a. The measurements derived using ELISA and subsequent statistical analysis clearly demonstrated that there is no significant difference between the levels of the novel proteins expressed by the stacked transgenic plant under evaluation and its parental genotypes.[1].
- b. There is an expected low expression of the novel proteins in the regulated stacked event under evaluation, similar to what is recorded in its parental genotypes.[1].

- c. The selectable marker genes *nptII* and *uidA* are transferred and expressed in the regulated stacked event at very low levels.[1].
- d. There is no possible interaction among the novel proteins introduced in Cotton MON 15985 × MON 1445. The stability of the genome/partial genome of the parentals in the stacked transgenic cotton has been demonstrated. The genetic material of the parentals, containing the novel genes, were stably incorporated in the stacked event. The protein level measurements done using ELISA and subsequent statistical analysis clearly demonstrated that there is indeed no significant difference among the expression levels of the novel proteins in the parentals and the transgenic stacked corn.[1].

### **STRP'S RECOMMENDATION**

In summary, the STRP agrees that the regulated article cotton MON 531 x MON 1445 is still safe and remains phenologically similar with conventional corn. [16][17]

### **BAI'S ASSESSMENT**

- a. The complete description of the mode of action of each gene product has been provided in the submitted technical dossiers [1].
- b. The mode of action of each gene product has been enumerated and differentiated.
  - 1) Cry1Ac and Cry2Ab2 - Cry proteins originated from the bacteria *Bacillus thuringiensis* and it targets the midgut lining of different insects thus it serves as a pest control.
  - 2) CP4 EPSPS - this protein is involved in the shikimate pathway of plants and reduces the binding affinity to glyphosate making it herbicide-tolerant.
  - 3) NPTII - is a selection protein, usually flanked with the gene of interest, where it metabolizes neomycin and kanamycin and further confirms the inserted gene for genetic transformation.
  - 4) β-D-glucuronidase or GUS protein is an enzyme that serves as a visual marker for the selection of successfully transformed plant cells [1][2][3][4][5][6].
- c. The involvement of each gene product in different metabolic pathways have been enumerated and differentiated.

- 1) CP4 EPSPS catalyzes the sixth step of the shikimate pathway of the plants to produce aromatic acids and compounds.
  - 2) Cry1Ac and Cry2Ab2 targets the midgut epithelial cells of the insects and they are usually expressed in the cytoplasm of cells that are present in the green parts of the plant.
  - 3) NPTII is a protein that is only used to select the transformed plant cells.
  - 4) GUS protein is a hydrolase that is involved in carbohydrate metabolic processes [1][4][5][7][8].
- d. Occurrence of unintended effects of the stacked genes on plant's metabolism is unlikely since these inserted genes have long established the history of safe use. It has been expressed in the submitted technical dossier and is supported by publications [1].

#### **BAI'S RECOMMENDATION**

Although in the Philippines cotton MON 15985 x MON 1445 was only applied for direct use, control measures during transport should be also considered by the developer to prevent dispersal of the volunteer plants and subsequent gene flow to the wild [16][17].

## BPI-PPSSD'S ASSESSMENT

### A. Metabolic Pathways

- a. The developer provided a complete description of the mode of action of CP4 EPSPS, Cry1Ac, Cry2Ab2, GUS and NPTII proteins [1].
- b. CP4 EPSPS proteins are involved in the biochemical shikimate pathway producing aromatic amino acid in the chloroplasts. It catalyzes the transfer of enolpyruvyl group producing inorganic phosphate and 5-enolpyruvylshikimate-3-phosphate. This mechanism is inhibited with glyphosate binding which blocks the binding of EPSPS to phosphoenolpyruvate (PEP). CP4 EPSPS, on the other hand, has higher affinity for PEP thus allowing the catalysis. Hofte and Whiteley (1989) described the mode of actions of insecticidal crystal (Cry) proteins of *Bacillus thuringiensis* [10]. Cry1 proteins including Cry1Ac and Cry2Ab2 are specific to lepidopterans. 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. NPTII protein, as a marker protein, catalyzes the phosphorylation of the hydroxyl group of aminoglycoside in aminoglycoside antibiotics such as neomycin and kanamycin.  $\beta$ -D-glucuronidase (GUS) protein catalyzes the hydrolysis of a range of the  $\beta$ -glucuronidase into their corresponding acids and glycones [1][9][10][11].
- c. The products are not involved in the same metabolic pathway. CP4 EPSPS proteins are involved in the shikimic acid pathway of aromatic amino acids. Cry proteins are not involved in metabolic pathways in plants. NPTII protein, as a marker protein, catalyzes the phosphorylation of the hydroxyl group of aminoglycoside in aminoglycoside antibiotics such as neomycin and kanamycin.  $\beta$ -D-glucuronidase (GUS) protein catalyzes the hydrolysis of a range of the  $\beta$ -glucuronidase into their corresponding acids and glycones [1][9][10][11].
- d. The expression of the proteins in cotton MON 15985 x MON 1445 is similar to the corresponding levels in single events except for NPTII which is expected since the stacked product contains both NPTII proteins from each of the single events. Results showed that the proteins are expressed similarly to the combined trait product as in its corresponding single events. Their distinct mode of action, involvement in different metabolic pathways, and the protein expression analysis indicates that the possibility of an unexpected effects of the stacked genes on the metabolism of the plant is unlikely [1][9][10][11][12][13][14].

### B. Post-Surveillance Report

In spite of the proponent's inability to provide the requested information by the DA - Biotech Committee (DA-BC) on the existing post-surveillance of the regulated articles in other countries that has approved its use as food, they presented in writing a rationale on why the countries such as Australia and New Zealand do not conduct post-market surveillance for food safety. FSANZ does not consider post-market surveillance for food safety as a practical and effective risk management option since the pre-market assessment should already address the issue on the safety of the GM product. In our case, MON 15985 x MON 1445, MON 88913 and H7-1 were already subjected to food safety risk assessment wherein based on the weight of evidence, the regulated articles are as safe as, and is substantially equivalent to its conventional counterparts.

Should the rationale for the post-market surveillance be that the GM product may pose long term adverse effects on human health, chronic health problems are influenced by a multitude of factors that are not specifically or solely associated with consumption of food. If this is the case, the relevance and impact of the data that will be attained should be proportional to the cost of establishment of analytical methods and infrastructures for the post-market surveillance.

Such justification is adherent to the multi-factor decision making approach indicated in FAO Guidance Materials for risk management wherein scientific information on health risks and other factors including economical factors are needed to be considered and weighed in selecting the preferred risk management actions such as the post-surveillance monitoring.

#### **BPI-PPSSD'S RECOMMENDATION**

After a thorough review of the new studies submitted by Monsanto Philippines, Inc. for cotton MON 15985 x MON 1445 application for direct use as food, feed and for processing, the BPI-PPSSD found that the new studies submitted by the applicant will not affect the safety of the regulated article. They have also noted that none of the studies had implications to food safety [16][17].

## **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 FFP of cotton MON15985 x MON1445, hereunder are the observations and appropriate actions:

1. The regulated article has been approved in the Philippines for direct use as food, feed, or for processing. The individual events have already undergone rigorous assessments on its safety for consumption and risk to the environment. Moreover, the individual events in the stacked trait have both been granted biosafety permits in the country [11][13][15];
2. The donor organism for CP4 EPSPS protein, *Agrobacterium* sp. strain CP4 is a common soil bacterium and is not pathogenic to humans and animals. Also, the CP4 EPSPS protein does not resemble any toxin or allergen. *Bacillus thuringiensis*, the donor organism for the Cry1Ac and Cry2Ab2 is also a common soil bacterium and is not likely to be pathogenic to humans and non-lepidopteran animals. These proteins are also not toxic or harmful to non-target organisms as established by safety-specific studies [11][13][15];
3. The stacked event was developed through conventional breeding of the transgenic parents, similar to breeding of non-transgenic parents. It also has no significant difference from the non-transgenic plants in terms of composition, aside from the genes introduced. Furthermore, the safety of the individual events has previously been established [11][13][15]; and
4. The project description report (PDR) discusses the specified environmental management plan indicating the possible risk and harm to the environment particularly on biodiversity and non-target organisms as well as the mitigating measures and contingency plan. Cotton cannot survive in unmanaged environments. Therefore, it is less likely to persist in case of unwanted release [11][13][15].

## **DENR BC'S RECOMMENDATION**

Based on the review and evaluation, the DENR-BC considered the regulated article safe to the environment, particularly on biodiversity and non-target organisms and hereby submits the technical report relative to the application of Monsanto Philippines, Inc. for Biosafety Permit for direct use as food, feed, or for processing of cotton MON15985 x MON1445. The submitted studies have been acknowledged by the DENR-Biosafety Committee [16][17].



## **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 cotton MON 15985 x MON 1445, the DOH-BC found that the regulated article applied for direct use as food, feed or for processing (FFP) is as safe as its conventional counterpart and shall not pose any significant risk to human health.

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 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 cotton varieties.
4. The regulated article is not materially different in nutritional composition from that of the non-transgenic cotton or the conventional cotton.

## **DOH BC'S RECOMMENDATION**

It is suggested that the Bureau of Plant Industry (BPI) ensure that there shall be clear instructions that the product is only for the purpose of direct use for FFP and is not to be used as planting materials.

The new studies provided are on the environmental and agronomic effects of GM cotton [16][17]. Based on the recommendation of Munive et al. (2018) [18] in their study entitled "*Evaluation of the impact of genetically modified cotton after 20 years of cultivation in Mexico*", "*Control measures need to be implemented during transport of the bolls and fiber to prevent dispersal of volunteer plants and subsequent gene flow to wild relatives distributed outside the GM cotton growing areas.*"

Hence, we recommend to include mitigating measures to prevent risk of volunteer plants and gene flow during transport as well as insect resistance as part of due diligence.

## **SEC EXPERT'S ASSESSMENT**

- a. Cotton is widely produced and consumed and is a significant component of global trade of agricultural commodities. However, the Philippines is producing a very minimal quantity of cotton. As discussed, there is an increasing trend of import of cotton from 2015-2019. On the other hand, the export data of the Philippines shows zero (0) exports in the same years. This implies that the Philippine cotton industry is highly dependent on cotton imports to meet the domestic demand for this commodity.
- b.**Based on the data provided by the applicant, the granting of permit to import cotton MON 15985 × MON 1445 will not drastically affect the current patterns of consumption, production, and trade of cotton. Granting permits to import MON cotton 15985 × MON 1445 for direct use as food, feed or for processing may help stabilize supply and prices of cotton. It will also help improve the supply chain structure and performance of cotton in the Philippines. With a stable supply of cotton, it will improve the efficiency and effectiveness of the supply chain of cotton. The improvement of the domestic supply chain will result in improved domestic trade. However, the global trade of cotton will not be affected since Philippine imports of cotton are very minimal relative to global trade.

## **SEC EXPERT'S RECOMMENDATION**

The SEC expert recommends for the approval and issuance of the biosafety permit of cotton MON 15985 x MON 1445.

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