ASSESSORS' CONSOLIDATED REPORT ON MONSANTO PHILIPPINES INC.' COTTON MON 88913 APPLICATION FOR DIRECT USE AS FOOD AND FEED, OR FOR PROCESSING

EXECUTIVE SUMMARY

On November 15, 2019, Monsanto Philippines Inc. submitted cotton MON 88913 for direct use, 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 Scientific and Technical Review Panel (STRP), Bureau of Animal Industry, and BPI Plant Products Safety Services Division concurred that cotton MON 88913 is as safe as its conventional counterpart.

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 MON 88913 is safe as its conventional counterpart and shall not pose any significant risk to human health.

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 UPLB. The SEC expert, on the other hand, was provided with special questionnaire on socio-economic, ethical and cultural considerations that have been addressed by UPLB in relation to their application.

INFORMATION ON THE APPLIED EVENTS

The purpose of this cotton MON 88913 biosafety permit application is for Direct Use as Food, Feed or Processing (FFP).

Monsanto has developed a second-generation glyphosate-tolerant cotton product, Roundup Ready® Flex cotton MON 88913, (hereinafter referred to as MON 88913) which provides increased tolerance to glyphosate during the critical reproductive phases of growth compared to Roundup Ready® cotton MON 1445. Use of MON 88913 will enable the application of a Roundup® agricultural herbicide over the top of the cotton crop at later stages of development than is possible with the current Roundup Ready® cotton product. This will provide more effective weed control options during crop production, because Roundup® agricultural herbicides are highly effective against the majority of annual and perennial weeds that can be problematic during the later stages of crop development, with minimal risk of crop injury.

Control of weeds in a cotton crop is essential because weeds compete with the crop for the same limited resources in the field including sunlight, water and nutrients. Because failure to control weeds within the crop can result in decreased yields and reduced crop quality, an intensive program for weed control is essential to ensure profitability. Losses from weeds in cotton result in a $300 million crop loss per year. In addition, weeds present at cotton harvest reduce the efficiency of the mechanical harvest of the crop and can reduce both the quality and value of the lint because of staining by vegetation.

MON 88913 was developed through *Agrobacterium tumefaciens*-mediated plant transformation using the same *cp4 epsps* coding sequence and chloroplast targeting sequence and produces the same CP4 EPSPS protein as Roundup Ready® cotton.

Approval of the permit for direct use for food, feed and for processing of cotton MON 88913 will help maintain global trade of cotton products that are imported into the Philippines for food, feed and for processing purposes.

Countries Where Approvals Have Been Granted

Country	Food	Feed	Cultivation
	direct use or processing	**direct use or processing**	**domestic or non-domestic use**
Australia	2006		2006
Brazil	2011	2011	2011
Canada	2005	2005	
China	2007	2007	
Colombia	2009	2008	
Costa Rica			2009
European Union	2015	2015	
Japan	2005	2006	
Mexico	2006		2006
New Zealand	2006		
Philippines	2005	2005	
Singapore	2014	2014	
South Africa			2007
South Korea	2006	2006	
Taiwan	2015		
United States	2005	2005	2004

Source: https://www.isaaa.org/gmapprovaldatabase/event/default.asp?EventID=56

STRP's Assessment

1. Host Organism

a. Cotton (*Gossypium hirsutum* L.) is a source of cottonseed oil and linters which are the primary products for human use. In the field of animal nutrition, cottonseed meal is principally sold as feed ingredient for livestock as source of protein [1][2].

b. Cottonseed contains anti-nutrient components and due to these, only highly refined products are for human consumption. This is because anti-nutrients are drastically reduced during processing. Cotton also contains gossypol and cyclopropenoid fatty acids which are toxic to non-ruminant animals and used as a protein supplement for ruminants [1][2][3][4][5][6][7][8][9].

2. Donor Organism

a. The donor organism of *cp4 epsps* gene *Agrobacterium sp.* strain CP4, has been previously reviewed for safety assessment of other Roundup Ready® crops and is not known toxic and allergenic to humans and animals [1][11][12].

b. CP4 EPSPS is not known to be toxic or allergenic by other global regulatory agencies. The CP4 EPSPS protein is functionally equivalent to native plant EPSPS except for lack of affinity for glyphosate [1][11][12].

3. Transformation System

a. *Agrobacterium*-mediated transformation of the genomic DNA has been done in cotton MON 88913 [1].

b. Cotton MON 88913 was produced with the double-border, binary vector PV-GHGT35. Plasmid vector PV-GHGT35 contains border regions that delineate the T-DNA to be transferred into cotton and are necessary for the efficient transfer of the T-DNA into the plant cell. This T-DNA contains two tandem *cp4 epsps* gene expression cassettes that were transferred into the cotton genome by *Agrobacterium tumefaciens* during the *in vitro* transformation process [1][13][14][15][16][17][18][19][20][21][22][23].

c. Results of Southern blot analysis show that a single copy of the T-DNA sequence was integrated into the cotton MON 88913 genome at a single integration locus [1][24].

d. The PCR analysis and DNA sequencing clearly confirmed the organization of the elements within the DNA insert in cotton MON 88913 and confirmed that there are no truncations, deletions or rearrangement after PCR analysis and DNA sequencing, thus, no novel open reading frames (ORFs) or polypeptides were created [1][24][25].

e. The transgene *cp4 epsps* has been expressed in other approved GM crops including soybean, sugar beet, alfalfa, maize, canola, and other cotton events [26].

f. Southern blot analysis indicates that cotton MON 88913 does not contain any detectable backbone sequence from the transformation vector PV-GHGT35 [1][24].

4. Food and Feed Safety

a. SDS-PAGE and western blot analyses were used to confirm that the CP4 EPSPS protein is digestible in simulated gastric fluid containing pepsin [1][27].

b. When subjected to heat treatment, results of functional activity assay, as well as an SDS-PAGE assay, show that CP4 EPSPS is inactivated in below 15 minutes [28].

c. Using ALLPEPTIDES database, results showed no similarity between the CP4 EPSPS protein and any known toxic or pharmacologically active proteins relevant to human or animal health [1][29].

d. Results of an acute oral mouse toxicity study revealed that there are no treatment-related effects on survival, clinical observations, body weight gain, food consumption, or gross pathology on tested mice up to 572 mg/kg [1][11][30].

e. FASTA sequence alignment tool was used to evaluate potential structural similarities between CP4 EPSPS protein and proteins in the allergen database (AD4). Results showed that there were no immunologically relevant sequences similar to the CP4 EPSPS protein present in cotton MON 88913 [29].

f. On the basis of western blot analysis, the electrophoretic mobility and immunoreactive properties of the plant-produced CP4 EPSPS protein were demonstrated to be comparable to those of the *E. coli*-produced CP4 EPSPS reference standard. Also, the plant-produced CP4 EPSPS protein is concluded to be equivalent to the *E. coli*-produced CP4 EPSPS reference standard, with respect to the absence of glycosylation [1][31].

g. The CP4 EPSPS protein represents only 0.12% of the total protein in MON 88913 [1].

h. A statistically significant difference was observed for moisture when cotton MON 88913 was compared to cotton MON 88913(-) through compositional analysis. However, the mean value was within the 99% tolerance interval for commercial varieties and literature ranges [1][4].

i. All sixteen commercial reference varieties produced a 99% tolerance interval for conventional cotton. The test mean values were all within the ranges established [1][4].

j. All test mean values of proximate were within or similar to literature ranges. There were no differences observed in proximate that were not biologically relevant from a food and feed safety perspective. Although there were statistically significant differences observed in parameters such as phenylalanine, tryptophan, 18:2 linoleic, 18:1 oleic acid and manganese, all the test values were still within 99% tolerance interval for commercial varieties and literature ranges [1][4].

k. There were no statistically significant differences observed for the anti-nutrients and all the test values were within the literature ranges [1][4].

STRP's Conclusion

After a thorough review of the new studies submitted by Monsanto Philippines Inc. for cotton MON 88913 application for direct use as food and feed, or for processing (FFP), the STRPs found that the new studies submitted by the applicant will not affect the safety of cotton MON 88913 [47][48][49]. It is good that the applicants are updating the reviewers regarding the recent developments, field trials and journal article publications that will have bearing on the previous safety evaluation of the application.

Furthermore, after a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines, Inc. relevant to cotton MON 88913, the STRPs found sufficient evidence that the regulated article applied for direct use will not pose any significant risk to human and animal health as its conventional counterpart. Any risks could be managed by strict implementation of processing protocols for the reduction/inactivation of the indicated anti-nutrients, particularly for products intended for human consumption.

BAI's Assessment

1. **Toxicological Assessment**

   a. SDS-PAGE assay results showed that 98% of the E. coli-produced CP4 ESPS was digested in 15 seconds using pepsin. There were also no visible fragments detected in the gel after the assay. It was confirmed by another test which is the western blot analysis [27].

   b. Through SDS-PAGE assay, it was observed that the protein weights were stable across lanes with reduced activity in elevated temperature [28].

   c. It was determined that the closely similar variants of the CP4 EPSPS are the ones from Zea mays (Sequence ID ARW80140.1) and Glycine max (AAL67577.1) both of which have 99.12% identity and were synthetic constructs. There was also no identified toxin similar to the Toxin and Toxin Target Database [29][32].

d. Acute oral gavage was performed and E. coli-derived CP4 EPSPS was administered in CD-1 female and male mice. The dosages for the procedure were 49, 154, and 572 mg/kg weight. There were no adverse findings that are relevant to the treatment thus, the established NOEL is at 572 mg/kg [30].

e. MALDI TOF and Immunoblot assays determined that CP4 EPSPS was indeed derived from E. coli and it is similar in properties compared to the ones expressed from cotton MON 88913 [35].

2. Allergenicity Assessment

a. Pepsin was used for the digestibility study and the T50 was identified to be below 15 seconds since 98% of the E. coli-produced CP4 EPSPS was digested in 15 seconds. After the assay, there were no visible fragments detected in the gel even after varying lengths of incubation. This was determined through SDS-PAGE in 10-20% acrylamide gel, with proteins stained with Brilliant Blue G. To further confirm if there were fragments, western blot analysis was conducted and it showed similar results with the SDS-PAGE assay [35].

b. The estimated T50 for CP4 EPSPS was below 15 minutes. This was determined by having the protein incubated in different temperatures: 25°C, 37°C, 55°C, 75°C, 95°C in 15 and 30 minutes. After the heat treatment, the protein samples were subjected to SDS-PAGE assay to evaluate its activity. It was observed that the protein weights were stable across lanes with reduced activity in elevated temperatures [32].

c. The provided amino acid sequence was aligned with the allergen sequences in the Allergen Online database, and there were no known allergens similar to the CP4 EPSPS. Furthermore, there were no identified matches greater than 35% in 80 mer Sliding Window. Its physico-chemical properties were determined through MALDI-TOF, western blot, SDS-PAGE, enzymatic activity, and glycosylation tests. CP4 EPSPS produced from MON 88913 and E. coli-derived was observed to be similar in terms of absence of glycosylation and molecular weight which was approximately 43 kDa, and its enzymatic activity to release phosphate groups.

3. Nutritional Data

a. Sixteen commercial varieties were grown in the same site under the same environmental conditions and the test mean values of proximate were within the established ranges and within or similar to literature range [1][4].

b. Phenylalanine, tryptophan, linoleic oleic and manganese show statistical significance but the values are within the tolerance interval of commercial varieties [1][4].

BAI's Conclusions

After a thorough scientific review of technical documents regarding new studies conducted on cotton MON 88913 submitted by Monsanto Philippines Inc. applied for direct use as food and feed, or for processing, BAI agrees with the applicant's claim that the gene modification will not affect the safety of cotton MON 88913 as supported by the new studies submitted by the applicant.

The three (3) new studies submitted by the applicant determined the yield, environmental/agronomic effects, and transgene concentration of MON 88913. Results showed that there was no reduction in the yield. There were also no observed effects on non-target organisms. Moreover, transgene concentrations in single events predicted similar concentrations in breeding stacks containing the single events. The studies showed no impacts to the original safety conclusions specifically in feed safety perspective [31][32][33].

Furthermore, after a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines, Inc. relevant to cotton MON 88913, BAI found scientific evidence that the regulated article applied for animal feed use is as safe as its conventional counterpart and shall not pose any significant risk to animal health.

BPI PPSSD's Assessment

1. **Toxicological Assessment**

    a. SDS-PAGE and western blot analyses demonstrated that CP4 EPSPS was rapidly digested upon incubation with simulated gastric fluid (SGF) with pepsin within 15 seconds [27].

    b. Heat stability assay through SDS-PAGE analysis demonstrated that the apparent molecular weight of CP4 EPSPS protein remained constant upon subject to temperatures ranging from 25˚C to 95˚C for 30 minutes [28].

    c. Amino acid sequence comparison with non-redundant protein sequences databases using BLASTP showed no significant homology of CP4 EPSPS to any known toxin [36][37].

    d. Acute oral gavage demonstrated that administration of 572 mg/kg bw CP4 EPSPS protein in mice did not yield any significant effects on survival, clinical observations, body weight gain, food consumption or gross pathology. The No Observed Effect Level (NOEL) for CP4 EPSPS is 572 mg/ kg bw [30].

    e. E. coli was used as the source of CP4 EPSPS protein for testing. The E. coli-produced CP4 EPSPS protein has been shown to be equivalent to the plant-produced CP4 EPSPS protein in terms of functional activity, structure, glycosylation and apparent molecular weight [35].

2. **Allergenicity Assessment**

a. SDS-PAGE and western blot analyses demonstrated that CP4 EPSPS was rapidly digested upon incubation with simulated gastric fluid (SGF) with pepsin within 15 seconds [27].

b. Heat stability assay through SDS-PAGE analysis demonstrated that the apparent molecular weight of CP4 EPSPS protein remained constant upon subject to temperatures ranging from 25˚C to 95˚C for 30 minutes [28].

c. Bioinformatics analysis using the full-length sequence, an 80-mer sliding window and 8-mer exact match in AllergenOnline.org database did not yield any significant homology of CP4 EPSPS to any known allergen above 35% shared identity [37][38].

3. Nutritional Data

a. Combined site analysis from four (4) different locations demonstrated no significant differences between the proximate levels in MON 88913 cottonseed and the negative segregant of cotton MON 88913 [4].

b. All mean values of proximate from combined site and individual site analyses were within the range of 16 commercial reference varieties grown under the same environment conditions in four different locations. They are also within the range of literature values and/or historical range for commercial varieties. [4].

c. Combined site analysis from four (4) different locations in US demonstrated no significant differences between the proximate levels in cotton MON 88913 cottonseed and the negative segregant cotton MON 88913(-) except for phenylalanine, tryptophan, oleic acid, linoleic acid and manganese [4].

d. Based on the statistical analyses, there were no statistical differences between the fatty acid, amino acid, vitamin E, mineral and fiber content of cotton MON 88913 and non-transgenic cotton that can be considered biologically relevant. All values are within the range of commercial varieties and literature values [4].

e. Combined site analysis and individual site analyses from four different locations demonstrated no significant differences between the gossypol and aflatoxin levels in cotton MON 88913 cottonseed and the negative segregant MON 88913(-) content [4].

f. Compositional analysis demonstrated biologically relevant differences in the levels of anti-nutrients between cotton MON 88913 and the conventional counterpart. Hence, the effect of the level of anti-nutrients in processed products of cotton MON 88913 is expected to be similar with the conventional counterpart. Processing reduces the anti-nutrient content of the product. No

adverse effects to humans have been attributed to the residual gossypol in properly processed refined, bleached and deodorized cottonseed oil [4][7][8][9].

4. 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 Conclusion

Upon evaluation of the documents provided by the proponent and scientific literature search conducted for the food safety risk assessment of cotton MON 88913, the following assessments were made:

History of safe use is attributed to the host organism (*Gossypium hirsutum*) and donor organism (*Agrobacterium* sp. strain CP4) which are not known to be toxic or allergenic to humans and animals.

Safety of the novel protein, CP4 EPSPS, in cotton MON 88913 was assessed based on the digestibility, heat inactivation, amino acid sequence comparison and oral toxicity studies provided by the developer. Results of the analyses indicated that the novel protein is being

digested rapidly in mammalian gastric fluid, a characteristic of dietary proteins. It is inactivated by induction of heat which is normally occurring during processing and cooking, and does not cause toxicity on mice via acute oral gavage. Amino acid sequence analysis indicated that CP4 EPSPS has no significant homology to any known toxins or allergens.

Safety assessment based on the nutritional data indicates that there is no significant difference between the proximate, fiber, amino acid, fatty acid, minerals, vitamin E and anti-nutrient levels of cotton MON 88913 and conventional cotton that can be considered biologically relevant.

Upon review of the provided materials of Monsanto Philippines, Inc. and other literatures, weight of evidences approach indicates that cotton MON 88913 is as safe as its conventional counterpart with regard to substantial equivalence and food safety [47][48][49].

ANNEX IV

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 and feed, or for processing (FFP) of cotton MON 88913, the DOH-BC found that the regulated article 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 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 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 Conclusion

After a thorough review of the new studies submitted by Monsanto Philippines, Inc. for cotton MON 88913 application for direct use as food and feed, or for processing (FFP), the DOH-BC found that the new studies submitted by the applicant will not affect the safety of cotton MON 88913 [47][48][49].

SEC Expert's Assessment

a. To date, the Philippines is not a cotton producer. It imports raw cotton which is composed of raw lint for fabrics and cotton seeds for animal feeds [42][43][44][45][46].

b. The focus of the SEC assessment is the trade of raw cotton which is further processed into limited fabric production and seed cotton for animal feeds. GM cotton for Direct Use as Food and Feed, or for Processing is favorable, economically to the Philippines [42][43][44][45][46].

SEC Expert's Recommendation

After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines, Inc., cotton MON 88913, the SEC expert recommends for the approval and issuance of biosafety permit of the said GM cotton.

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