ASSESSORS' CONSOLIDATED REPORT ON MONSANTO PHILIPPINES INC.'s APPLICATION FOR DIRECT USE AS FOOD AND FEED, OR FOR PROCESSING OF COTTON MON88702

EXECUTIVE SUMMARY

On July 16, 2019, Monsanto Philippines submitted cotton MON88702 application for direct use 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 STRP, BAI, and BPI-PPSSD found scientific evidence that cotton MON88702 is as safe as its conventional counterpart and shall not pose any significant risk to human and animal health.

The Department of Environment and Natural Resources – Biosafety Committee (DENR-BC), after a thorough scientific review and evaluation of the accomplished Project Description Report (PDR) and Environmental Risk Assessment (ERA) form along with the submitted sworn statement and accountability of the proponent, reported that the direct use of the regulated article will not cause any adverse effect on the environment (land and water) and biodiversity.

The DOH-BC, after a thorough scientific review and evaluation of documents related to Environmental Health Impact, found scientific evidence that the GM application will not cause significant adverse effects to human and animal health, is unlikely to result in allergenic reaction, and is as safe as food or feed derived from conventional varieties.

Furthermore, the Socio-economic, Ethical and Cultural (SEC) expert, after reviewing thoroughly the accomplished SEC questionnaire, also recommended for the issuance of Biosafety Permit.

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

STRP'S ASSESSMENT

1. Host Organism

a. Whole cottonseed and its derivatives are rich sources of key nutrients. Aside from the whole cottonseed which is high in dietary fiber, its derivatives namely cottonseed oil and cottonseed meal, hulls and linters are also a pure source of essential fatty acids, amino acids and minerals. [1][2].

b. Among the reported antinutrients present are gossypol and cyclopropenoid, where gossypol binds with dietary lysine thus interfering its bioavailability which may lead to lysine nutritional deficiency causing related health problems. On the other hand, cyclopropenoid fatty acids interfere with the metabolism of saturated fats also causing some related health issues in animals. [1][2][3][4][5][6][7][8][9].

c. The toxicants present in cotton plants are gossypol and cyclopropenoid fatty acids (CPFAs). These toxicants affect non-ruminant animals more since ruminant animals detoxify them through digestion in their rumen. Reports show that toxicity was exhibited when large amount of cottonseed meal were fed. Thus, these compounds narrow down the potential use of cottonseed as a protein supplement in animal feed. [1][2][3].

d. Although allergy to cottonseed is not a frequent occurrence, individuals may experience a reaction to cottonseed oil that may have symptoms involving both the skin and respiratory system. This allergy is due the 2S protein, a water-soluble protein, that may cross over acidic stomach mucous barriers to cause inflammation to the mucosal immune system, which provokes an allergic reaction in certain individuals. This is why highly processed cottonseed oil is recommended as such processing eliminates this allergen. [1][2][3][10][11][12].

2. Transgenic Plant

a. MON88702 has been approved for food use in Australia (2018), Canada (2018), Japan (2019), New Zealand (2018), Taiwan (2019) and United States (2018) [13].

b. MON88702, contains the *mCry51Aa2* expression cassette, which is responsible for the mCry51Aa2 protein. This has 96% sequence similarity to the amino acid sequence of wild-type Cry51Aa2 from *Bacillus thuringensis*. Many literatures have been published to attest to the safety of *Bacillus thuringiensis* and their insecticidal protein, which includes Cry proteins. Some strains have been used to control mosquitoes and blackflies while others were used to maintain quality drinking water for human. Additionally, bioinformatics tools have shown that the protein-encoding sequences do not share relevant similarities with allergens, toxins or biologically active proteins that may be of concern. [14][15][16][17][18][19][20][21][22][23][24].

3. *Donor Organism*

a. The donor organism is *Bacillus thuringiensis* and is not known to be toxic or allergenic. This bacterium is commonly found in soil and has been commercially used to produce microbial-derived products with insecticidal activity. In addition, microbial pesticides containing *Bt* Cry proteins have gone through extensive toxicity testing and have shown no adverse effects to human health.
b. There are no confirmed cases of allergic reactions to Cry proteins in microbial-derived *Bt* products for the past five decades of its utility. [1][24][25][26][27].

4. *Transformation System*

a. MON88702 was produced by Agrobacterium-mediated transformation using two transfer DNAs (TDNA) contained in the transformation plasmid, PV-GHIR508523 [1].

b. The first T-DNA, designated as T-DNA I, contains the mCry51Aa2 expression cassette, which expresses the mCry51Aa2 protein; while the second T-DNA, designated as T-DNA II, contains the aadA expression cassette [1].

5. *Inserted DNA*

a. Molecular characterization of the genetic modification in MON88702 was conducted using a combination of sequencing, PCR, and bioinformatics. The results of this characterization demonstrate that MON88702 contains a single copy of the intended T- DNA containing the *mCry51Aa2* expression cassette that is stably integrated at a single locus and that no plasmid backbone sequences or T- DNA II are present in MON88702. [1][26].

b. Bioinformatics analysis revealed that no novel chimeric open reading frames (ORFs) were formed in MON88702 [28].

6. *Genetic Stability*

The analysis demonstrated the stability of the DNA insert over multiple generations. The expected single identical pair of junction sequences observed as a result of the insertion of PV-GHIR508523 T-DNA I at a single locus in the genome of MON88702 has been retained across five breeding generations. [1][26].

7. *Expressed Material*

Segregation analyses show heritability and stability of the insert across multiple generations [1][20].

8. *Toxicological and Allergenicity Assessment*

a. Results of Western blot analysis revealed that intact mCry51Aa2 protein was present throughout the incubation time in pancreatin but with reduced intensity and protein fragments over time. This characteristic behavior is similar with other Cry proteins such as Cry3Bb1, Cry1Ac, and Cry1A.105. Sequential digestion of mCry51Aa2 protein using both pepsin and pancreatin was also done using SDSPAGE and Western blot analyses to further assess its susceptibility to gastrointestinal digestion enzymes. Results of SDS-PAGE showed that the mCry51Aa2 protein was digested within 2 min incubation time in pepsin while complete digestion of ~4kDa small transient protein fragments in pancreatin was observed within 0.5min. Western blot analysis, on the other hand, showed that mCry51Aa2 protein was digested within 2min of pepsin exposure. [29].

b. The result of heat inactivation study demonstrated a predictable protein tendency of denaturation and loss of functional activity at higher temperature. [30].

c. Bioinformatics analyses were performed to assess the potential toxicity of the mCry51Aa2 protein sequence. The results showed that there is a 28% similarity with GI1102943401, which is an aerolysin. However, it does not exhibit similarity in the receptor-binding domain, which is vital in identifying the identity of the target receptor within the entire mode-of-action. Thus, the alignment of mCry51Aa2 with GI1102943401 did not provide any information to indicate mCry51Aa2 to be toxic towards organisms other than the intended hemipteran and thysanopteran insect pests. [21][31].

d. The result of the acute oral gavage showed that there were no treatment-related effects on survival, clinical observations, body weight gain, feed intake and gross pathology [32].

e. FASTA sequence alignment program and an eight-amino acid sliding window search in conjunction with the "COMprehensive Protein Allergen REsource" (COMPARE) database were used to assess the potential for allergenicity of the mCry51Aa2 protein. The results showed that, there is no structurally and immunologically relevant similarities between the protein sequences of mCry51Aa2 and known allergens, gliadins, and glutenins. [31][33][34].

9. Nutritional Data

a. Proximate analysis showed that the difference in protein composition of cottonseed of MON88702 and conventional control was within the natural variability. Meanwhile, all proximate parameters were within the range values reported in literature and ILSI. [1][35][36].

b. Seven fatty acids (i.e. lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, arachidic acid, behenic acid) were observed for compositional difference between that in the cottonseed of MON88702 versus the conventional cotton control. While lauric acid has unavailable values in literature and ILSI Crop Composition Database (ILSI-CCDB), the other six fatty acids, were found within the natural variability of these respective components as published in the scientific literature on cotton composition and/or the ILSI-CCDB. Calcium mean

level of cottonseed of MON88702 was also found to be within the natural variability of this component as published in the scientific literature on cotton composition and/or the ILSI-CCDB. [1][35][36].

c. There were no significant differences in seed anti-nutrient levels between MON88702 and the conventional control. [35].

STRP'S RECOMMENDATION

STRPs find scientific evidence 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 greater risk to human and animal health.

BAI'S ASSESSMENT

1. Host Organism

a. Cottonseed has anti-nutrients such as gossypol and cyclopropenoid. Given that it has anti-nutrients, only thoroughly refined products are suitable for human consumption. [1].

b. The anti-nutrients components of cotton are considered to be toxic specifically to non-ruminant animals as per literature. With this, cotton is only fed to ruminants.

c. Cotton is not a source of allergens since cotton is primarily used for textile according to the literature provided. Aside from textile use, cotton is also notable for its importance in feed and human food such as oil and linters. With that, only the thoroughly processed cotton is being consumed and there were no allergic reactions reported based from the data available. Although inhalation of cotton dust can lead to asthma-like conditions called byssinosis. [1][2].

2. Transgenic Plant

Since MON88702 is substantially equivalent in nutrition and safety to its conventional counterpart, consumption pattern of cotton will not be affected by the introduction of MON88702 [1].

3. Donor Organism

Bacillus thuringiensis was the sole donor organism and is not known to be toxic or allergenic. Also, it has a long history of safe use [25].

4. Transformation System

MON88702 was produced by Agrobacterium-mediated transformation using two transfer DNAs (TDNA) contained in the transformation plasmid, PV-GHIR508523. The first T-DNA, designated as T-DNA I, contains the mCry51Aa2 expression cassette, which expresses the mCry51Aa2 protein; while the second T-DNA, designated as T-DNA II, contains the aadA expression cassette. During transformation, both T-DNAs were inserted into the cotton genome. [1].

5. Toxicological and Allergenicity Assessment

a. The results from the digestibility study suggests that mCry51Aa2 protein is rapidly digested in pepsin thus, is unlikely to cause adverse effects in animals when ingested [29].

b. Heat inactivation study revealed that, the estimated T50 result for the mCry51Aa2 protein is within 15 minutes at above 55ºC. This result was obtained using insect bioassay and SDS-PAGE. The insect bioassay conducted was to assess the impact of temperature on the functional activity of mCry51Aa1 protein while the SDS-PAGE was to evaluate the impact of temperature on protein integrity. Heat treated samples exceeding 75ºC showed decrease in molecular weight upon subjecting to SDS-PAGE. [30].

c. mCry51Aa2 protein in MON88702 significantly aligned with aerolysin toxin family protein. However, the alignment found between mCry51Aa2 and GI1102943401 which is an aerolysin toxin family protein did not provide sufficient evidence for the inserted protein to be concluded as toxic other than to intended pests. Aerolysin is a cytolytic pore forming toxin and generally described as pore forming, hence, the alignment. [21][31].

d. Acute oral gavage was performed, and the obtained NOEL is considered to be 5000mg/kg bw [32].

e. Result of the bioinformatics analysis suggests that mCry51Aa2 protein is not structurally and immunologically similar to any known allergens, gliadins, and glutenins [33][34].

6. Nutritional Data

a. Proximate analyses showed that there is a significant difference for protein in cottonseed but was within the natural variability according to ILSI-CCDB. Thus, it is not considered biologically meaningful from a food and feed safety or nutritional perspective. [1][35].

b. All test values of proximate were within or similar to literature and ILSI ranges [1][35].

c. Significant differences were found for seven fatty acids namely lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, arachidic acid, and behenic acid. However, these differences were less than the conventional range values. Moreover, the mean levels of the fatty acids were within the literature value except for lauric acid for which literature values were unavailable. As for calcium, difference was observed but was within the literature value. With all the data provided, it can be concluded that MON88702 is substantially equivalent with the conventional cotton. [1][35][36].

d. There were no significant differences in seed anti-nutrient levels between MON88702 and the conventional control [1][35].

BAI'S RECOMMENDATION

BAI find 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 human and animal health.

BPI-PPSSD ASSESSMENT

1. ***Host Organism***

   a. Cotton by-products are used as food. Although a minor component of dietary daily intake, cotton by-products are consumed by humans as food or food ingredients. Cottonseed oil is the primary cotton product used for human consumption.

   b. The crude oil about 2% non-glyceride materials was then removed during processing. Raw cotton fiber is processed extensively before its final use in products. After mechanical delinting, linters are converted to brown stock with an alkaline wash and temperatures >100^{o}C. Further processing steps denature or remove any protein, either endogenous or introduced into the cotton plant by genetic modification. Therefore, fiber used for food is not expected to contain any detectable genetic material or protein. [2].

2. ***Transgenic Plant***

   a. MON88702 has been approved for food use in Australia (2018), Canada (2018), Japan (2019), New Zealand (2018), Taiwan (2019) and United States (2018) [13].

   b. The consumption pattern in the overall population or any population sub-groups will not be changed, as MON88702 will be used in the same ways as the other conventional cotton [1].

3. ***Donor Organism***

   Bacillus thuringiensis was the sole donor organism and is not known to be toxic or allergenic. Also, it has a long history of safe use [25].

4. ***Transformation System***

   a. *mcry51Aa2* gene in MON88702 cotton is derived from *Bacillus thuringiensis*, a common soil bacterium.

   b. History of safe use is attributed to the donor organism as it is commonly used in previously assessed single events [25].

5. ***Toxicological and Allergenicity Assessment***

a. Results of the digestibility study showed that mCry51Aa2 was rapidly degraded in SGF and the remaining fragments were completely degraded in pancreatin. The estimated $T5_0$ result is below 0.5 minutes. [29].

b. SDS PAGE analysis showed that the band intensity of mCry51Aa2 protein remained constant at 25, 37 and 55ºC for 15 minutes. Decrease in the band intensity and molecular weight was observed upon subjecting to 75 and 95ºC for 15 minutes. Functional activity assay demonstrated the >95% reduction in functional activity of mCry51Aa2 upon subjecting to temperatures greater than 55 ºC within 15 minutes. [30].

c. Bioinformatics analysis indicated that mCry51Aa2 protein has no structurally relevant similarities to any known toxin [21][31].

d. Acute oral gavage demonstrated that administration of 5000 mg/kg bw mCry51Aa2 protein in mice did not result in any treatment-related effects on survival, clinical observations, body weight gain, food consumption or gross pathology. [32].

e. Data demonstrate the lack of both structurally and immunologically relevant similarities between the protein sequences of mCry51Aa2 and known allergens, gliadins, and glutenins.

6. Nutritional Data

a. Based on the statistical analyses, there were no statistical differences between the proximate analysis of MON88702 cotton and non-transgenic cotton that can be considered biologically relevant. All values are not significantly different and within the range of literature values indicating nutritionally not relevant. [1][35].

b. Based on the information, none of the differences in key nutrients is biologically meaningful. All values are not significantly different and within the range of literature values indicating nutritionally not relevant. [35].

c. Based on the statistical analyses, there were no statistical differences between the antinutrient content of MON88702 cotton and non-transgenic cotton that can be considered biologically relevant. All values are not significantly different and within the range of literature values. Hence, no food safety concern is being raised. [35].

BPI PPSSD'S RECOMMENDATION

Find scientific evidence that the regulated article applied for food and feed use is as safe as its conventional counterpart and shall not pose greater risk to human and animal health.

DENR BC'S ASSESSMENT

After a comprehensive review and evaluation of the documents including the scientific evidence from provided references and literature submitted by Monsanto Philippines, Inc., on its application for Direct Use as FFP of Cotton MON88702 hereunder are the observations:

1. 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, and water) and non-target organisms. The transgenic crop will not increase its weediness potential in case the seeds spill out into the environment because cotton has limited potential to survive outside agricultural settings, and the introduced genes are not expected to increase its ability to spread and persist. [37].

2. The mode of action of Cry protein product produced by the transgenic crop is well understood and it is not a known toxic to people, other vertebrates, and non-target invertebrates. Also, the conventional counterpart of Cotton MON88702 produces natural toxins as a defense against herbivory such as gossypol and cycloprenoid fatty acids. The introduction of mCry51Aa2 protein in the cotton is not expected to have increased the levels of natural toxins. [38].

3. 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. Furthermore, 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 considering that cottons have no potential to persist in an unfavorable environment. [39].

DENR BC'S RECOMMENDATION

Based on the review and evaluation, the DENR-BC considered the regulated article safe to the environment and non-target organisms.

DOH BC'S ASSESSMENT

The DOH-BC, after thorough review of the documents, find 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 and animal health and environment.

The following are the observations:

1. Pieces of scientific of evidence 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 in allergic reaction.
3. The regulated article is 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.
5. 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.
   [1][40].

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.

SEC EXPERT'S ASSESSMENT

1. Approval of the Insect Protected Cotton MON 87702 for direct use as food and feed, or for processing will help meet the increasing domestic demand of cotton in the country. As shown in the data submitted by the developer of the technology, domestic production of cotton had been declining over the past decades already, but the demand is increasing due to increasing population. In terms of production, it will not affect since the Philippine has only about 1,000 hectares of planted to cotton. Approval of Insect Protected Cotton MON 87702 may help stabilize the market condition of cotton. [41][42].

2. The approval of Insect Protected Cotton MON 87702 will not change drastically the current patterns of production, consumption/utilization of cotton in the Philippines. As claimed by the developer of the technology and data from Philippine Statistics Authority, Philippine production of cotton had been declining over the years while importation of cotton is increasing. The approval of the Insect Protected Cotton MON 87702 will ease the pressure of prices of cotton and cotton due to increasing demand. Likewise, consumption pattern would likely improve due to availability of cotton in the domestic market. [41][42].

3. The entry of Cotton MON88702 in the country will not affect the cultural practices of Filipino farmers since it will not be cultivated locally. In addition, Philippine production of cotton is very minimal. [41][42].

SEC EXPERT'S RECOMMENDATION

The SEC expert recommend for the approval and issuance of the Biosafety Permit of the GM product.

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