ASSESSORS' CONSOLIDATED REPORT ON MONSANTO PHILIPPINES' APPLICATION FOR DIRECT USE AS FOOD AND FEED, OR FOR PROCESSING OF CORN MON 87429

EXECUTIVE SUMMARY

On June 25, 2020, Monsanto Philippines submitted corn MON 87429 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 corn MON 87429is 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 corn MON 87429 is safe as its conventional counterpart and shall not pose any significant risk to human health.

The Department of Environment and Natural Resources – Biosafety Committee (DENR-BC), after a thorough scientific review and evaluation of documents and scientific evidence from literature of corn MON 87429, considered the regulated article safe to the environment, particularly on biodiversity and non-target organisms.

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

STRP'S ASSESSMENT AND CONCLUSION

A. Host Organism

Corn grain and forage, as well as the processed versions of them, are consumed as food for humans and feed for animals. In some regions in the Philippines, corn is used as an alternative to rice. It has been proven to be safe and is not considered a source of toxicants. Aside from being a good source of carbohydrates, it is also rich in polyunsaturated fatty acids oleic and linoleic acid [1][2].

Phytic acid, raffinose and trypsin inhibitor are the antinutrients found in Corn MON 87429 at very low levels. The levels of these antinutrients are comparable to the amount found in conventional corn [1][3].

B. Prior Safety Approval

Although MON 87429 is not found on ISAAA's GM approval database, Brazil has approved this event for use as food and feed, as well as cultivation in 2019. The explanation and the references provided are sufficient to support their claim that the novel article, MON 87429, is already approved for use as food in other countries abroad and the proponents were able to provide summary of existing documents and references [4][5].

C. Donor Organism

The introduced genes to corn MON 87429 are pat, dmo, ft_t, and cp4 epsps genes. The dmo gene is derived from the bacterium *Stenotrophomonas maltophilia* strain DI-6, with no pathogenicity in otherwise healthy humans and animals. The pat gene is derived from the bacterium *Streptomyces viridochromogenes,* a soil-borne microorganism, again with no recorded allergenicity issues. The donor organism for cp4 epsps is *Agrobacterium* sp., widely recognized as non-pathogenic nor allergenic. The ft_t gene is a modified version of the *Rdpa* gene from *Sphingobium herbicidovorans*, widely found in the natural soil environment. The gene expresses the FT_T protein, which itself is a modified version of the R-2,4-dichlorophenoxypropionate dioxygenase (RdpA) protein. No harmful effects were recorded if humans or animals were exposed to *Sphingobium* [3][6][7][8][9].

DMO, PAT (pat), FT_T, and CP4 EPSPS are not known to be toxic or allergenic. DMO protein are commonly found in many plants and consumed by animals without reports of adverse effects; PAT protein has no reports of animal adverse effects since the use of GMO crops expressing PAT in 1995. FT_T protein is an alpha-ketoglutarate-dependent dioxygenase. This type of protein has been identified in a broad range of organisms including bacteria, fungi, plants, and vertebrates, which have been extensively consumed by animals without reports of adverse reaction. CP4 EPSPS protein safety and mode-of-action is well documented and available in several publications [10][11][12][13][14][15][16][17][18][19][20][21].

D. Transformation Event

The transformation method used is *Agrobacterium*-mediated transformation, while the target of gene modification is the Genomic DNA [3].

Plasmid vector PV-ZMHT519224 was used in the transformation of maize to produce MON 87429. Plasmid vector PV-ZMHT519224 is 17776 kb in length and contains a single T-DNA that is delineated by Right and Left Border regions. The T-DNA contains the *pat, dmo, ft_t,* and *cp4 epsps* expression cassettes. During transformation, the T-DNA was inserted into the maize genome [3].

Results of NGS and bioinformatics analyses show that MON 87429 contains a single copy of the intended T-DNA that is stably integrated at a single locus and that no plasmid backbone sequences are present in MON 87429 [3][22].

PCR and DNA sequence analysis show that there were observed deletions in MON 87429 upon T-DNA integration. Such deletion due to Double Strand Break (DSB) is common during *Agrobacterium*-mediated plant transformation and is naturally occurring in plants and other eukaryotes during recombination processes. Additionally, the plant also has natural DSB repair mechanisms that makes it overcome detrimental effects of the lost genomic sequence [3][22][23][24].

Bioinformatics analyses show that the deletion and insertions detected will not produce any novel nor chimeric ORF nor expressed polypeptide associated with it [3][22].

While the novel proteins DMO, PAT and FT_T have no apparent metabolic role and is not directly involved in any metabolic activities in the corn plant, CP4 ESPS is involved in an anabolic pathway. CP4 EPSPS protein that is produced in the transgenic plant is insensitive to glyphosate. Thus, reconstituting Shikimate pathway and conferring resistance to the herbicide by the plant [3][10][15][25][26][27][28][29][30][31][32][33][34][35].

E. Food and Feed Safety

The SDS-PAGE followed by western blot analysis clearly demonstrated that the DMO protein, PAT protein, FT_T protein, and CP4 ESPS protein are digestible using pepsin and pancreatin as digesting enzymes.[3][6][36][37][38][39].

The protein activity and SDS-PAGE analyses detection clearly demonstrated that DMO, PAT, and FT_T is indeed functionally inactivated and degraded by heat treatment at 55°C and above at 15 min or beyond, while the same analyses demonstrated the inactivation of the CP4 EPSPS protein at temperatures above 75°C for exposures at 15 minutes [3][6][40][41][42][43].

Bioinformatics analyses show that DMO, FT_T and CP4 ESPS have no significant homology with known toxins. FASTA sequence alignment comparison of PAT protein

with toxin and protein databases, specifically TOX_2018 and PRT_2018, respectively, resulted to 23 alignments from which 18 displayed an E-score of ζƮe-5. PAT protein sequence displayed alignment with that of a toxin component of GNAT (GCN5-related N-acetyltransferase) toxin-antitoxin system of bacteria; however, this do not necessarily indicate that PAT protein is harmful to humans and animals [3][6][44][45][46][47].

The results of acute oral gavage shows that there were no test substance-related differences in mean body weights, mean body weight changes, or mean food consumption when MON 87429 DMO protein was administered by oral gavage at a dose of 1000 mg/kg body weight in male and female CD-1 mice. This is the same for PAT (pat) protein and FT_T protein that were both administered at a dose of 2000 mg/kg body weight in male and female CD-1 mice. There were also no treatment related adverse effects observed in animals dosed with CP4 EPSPS protein at 572 mg/kg body weight [3][14][48][49][50].

E. coli-produced DMO protein, PAT protein, FT_T protein, and CP4 ESPS protein were used for the safety assessment. Based on the results, the E. coli-produced DMO protein, PAT protein, FT_T protein, and CP4 ESPS protein have been shown to be equivalent to the plant corresponding protein present in MON 87429 [3][51][52][53][54].

The genes expressing each novel protein has a distinct promoter region and thus is assumed to be expressed independently of each other. Further, the equivalency tests conducted with each MON 89429 protein with the corresponding *E. coli* equivalent showed that functional activities are approximate of each other, except for DMO and CP4 EPSPS. The MON 87429 CP4 EPSPS has a lower purity than the bacterial equivalent, which may explain the discrepancy. The DMO proteins expressed by GM maize and *E. coli* have approximate purity but have widely varying functional activities. All values were within the ranges specified in the report [3][51][52][53][54].

The DMO, FT_T and CP4 EPSPS proteins are expected to accumulate in the chloroplast. In contrast, no such contiguous sequence is observed in the pat gene, and the expressed PAT protein then is assumed to accumulate in the cytoplasm[2].

In comparison with its conventional untransformed counterpart, the values yielded by MON 87429 through proximate analysis are statistically different. However, both are still within the range of values in literatures and therefore is considered not biologically relevant in terms of food and feed safety perspective [3][55].

MON 87429 contains statistically more palmitic, palmitoleic, stearic, linoleic, linolenic and behenic acids than the control but it contains significantly less oleic acid than the control. In terms of minerals, MON 87429 contains statistically less copper, iron, magnesium, and vitamin E than the control. The proximate analysis results show that the differences are not biologically relevant because the differences are much smaller than the range (maximum-minimum) reported for each parameter in MON 87429 [3][55]

The difference between the anti-nutrient composition of MON 87429 and its conventional counterpart is not considered to be biologically significant because all the values yielded from the proximate analysis are within the known range of values [3][55].

F. STRP's Conclusion

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

BAI'S ASSESSMENT AND CONCLUSION

A. Toxicological Assessment

Digestibility test using Brilliant Blue G Colloidal stained SDS-page gel and Western Blot analysis for both enzymes proved that DMO protein, PAT protein, and CP4 ESPS protein are readily degraded in either pepsin or pancreatic enzyme unlikely to pose a human and animal health concern. In the case of FT_T protein, it was readily degraded in pancreatic enzyme but not in pepsin enzyme alone. However, during the sequential digestion, pepsin enzymes became easily degraded. [3][6][36][37][38][39].

Dicamba monooxygenase assay and SDS-page assay show that DMO protein, PAT protein, FT_T protein, and CP4 ESPS protein will lose their functional activity but remain an intact protein when subjected to high temperature. [3][6][40][41][42][43].

A comparison of the FT_T protein sequence was performed with toxin databases, and the results show that DMO protein, FT_T protein, and CP4 ESPS protein have no biological sequence similarities with any other known toxins or other biologically active proteins of concern. In the case of PAT protein, there were 23 alignments with bacterial toxin-antitoxin system proteins. However, this does not provide any indication that the PAT protein would adversely impact human or animal health [3][6][44][45][46][47].

Results of acute oral toxicity of DMO protein, PAT protein, FT_T protein, and CP4 ESPS protein showed that there were no observable treatment-related effects on survival, body weight gain, food consumption or any clinical and pathological changes on the experimental animal [3][14][48][49][50].

The equivalence of the MON 87429-produced and *E. coli*-produced CP4 EPSPS proteins, MON 87429-produced and *E. coli*-produced DMO proteins, MON 87429-produced and *E. coli*-produced PAT proteins, and MON 87429-produced and *E. coli*-produced FT_T proteins were compared and the results of the assessments show that the characterized *E. coli*-produced CP4 EPSPS proteins, DMO proteins, PAT proteins, and FT_T proteins were established to be equivalent to the CP4 EPSPS protein, DMO protein, PAT protein, and FT_T protein isolated from grain of MON 87429 [3][51][52][53][54].

Results of SDS-PAGE analysis and the western blot analysis imply that the protein will likely be rapidly degraded in gastric/intestinal condition and is therefore unlikely to pose animal health concerns [36].

Proximate analysis results indicate that the only significant difference from the control was observed for total fat, the difference was -0.12% dw, but is within the 99% tolerance intervals for the population of conventional references and within the range of values found in the ILSI CCDB and published scientific literature. Also, the differences are not relevant from a feed safety perspective [3][55].

B. Nutritional Data

The mean levels of the six fatty acids, copper, iron, magnesium and vitamin E were within the natural variability of their respective range of values found in the ILSI CCDB and published scientific literature. Also, the differences are not relevant from a feed safety perspective [3][55].

Oleic acid, copper, iron, magnesium and vitamin E content of MON 87429 is significantly lower compared to the control while palmitoleic acid, stearic acid, linoleic acid and behenic acid are significantly higher but is within the 99% tolerance intervals for the population of conventional references and within the range of35 values found in the ILSI CCDB and published scientific literature. Also, the differences are not relevant from a feed safety perspective [3][55].

Levels of anti-nutrient in MON 87429 are compositionally equivalent to that of the conventional maize[3][55].

c. Conclusion

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

BPI PPSSD'S ASSESSMENT AND CONSLUSION

A. Toxicological and Allergenicity Assessment

SDS Page and Western Blot Analyses show that DMO protein, PAT protein, FT_T protein, and CP4 EPSPS are all easily digested in pepsin or pancreatin [3][6][36][37][38][39].

Heat activity assessment of *E. coli* - produced DMO protein, PAT protein, FT_T protein, and CP4 ESPS protein through functional assay and SDS PAGE at varying temperatures (25, 37, 55, 75, and 95 °C) showed that, at 55°C and above, the activity of DMO protein were observed to be at 0% [3][6][40][41][42][43].

Amino Acid Sequence Comparison with non-redundant protein sequences database using BLAST showed no significant homology of DMO, FT_T and CP4 EPSPS to any known toxin (BLAST). For PAT, results showed showed 23 alignments, 18 with E-score of ≤1e-5 was observed using the TOX_2018 database. Based on the study conducted by Herouet et al., alignments with bacterial toxin-antitoxin system proteins does not provide any indication that it has an adverse effect on human health. Similar results were yielded upon conducting amino acid sequence comparison with non-redundant

protein sequences database using BLASTp (BLAST) [3][6][61][44][45][46][47].

Acute oral toxicity study of DMO protein, PAT protein, FT_T protein, and CP4 ESPS protein indicated no treatment-related effects on survival, clinical observations, body weight gain, food consumption or gross pathology [3][14][48][49][50].

DMO, PAT, FT_T, and CP4 EPSPS proteins are expressed independently of each other since their corresponding genes are regulated by different promoters such as P-Clj.Ubq, P-Ea.Ubq, P-Ad.Ubq, and P-35S, respectively. Functional activities of these proteins are maintained [3][51][52][53][54][65].

B. Nutritional Data

Based on the statistical analyses, there were no statistical differences between the proximate levels of MON 87429 corn and non-transgenic corn that can be considered biologically relevant since all values are within the range of literature values [55].

Based on the statistical analyses, there is no differences in the key nutrients of MON 87429 and the conventional corn that can be considered as biologically relevant [55].

Compositional analysis demonstrated no significant differences among the anti-nutrient and secondary metabolite levels of MON 87429 corn and the non-transgenic counterpart [55].

C. Conclusion

Upon review of the provided materials of Monsanto Philippines, Inc. and other literatures, weight of evidences approach indicates that MON 87429 corn is as safe as its conventional counterpart with regards to substantial equivalence and food safety.

DOH-BC'S ASSESSMENT AND CONSLUSION

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 of Direct Use as Food, Feed or for Processing (FFP) of Corn MON 87429. DOH-BC 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 and recommendations:

1. Maize is the world's third leading cereal crop, following wheat and rice. It is grown as a commercial crop in over 25 countries worldwide. Field maize and its products are used in food products (e.g. oil, grits, meal, flours, ethanol, syrup and starch) and feed (e.g. hulls, gluten and hominy). Sweet maize and its products are used in food (e.g. kernels and meal) and feed (hulls, 60-65 % of volume). Popcorn maize kernels are used for popcorn and as basis for confections [1].

2. *Stenotrophomonas maltophilia* strain DI-6, which is the source of the *DMO*

gene, is an aerobic environmentally ubiquitous gram-negative bacterium commonly present in aquatic environments, soil, and plants. It can be found in healthy individuals without causing any harm to human health and infections in humans caused by *S. maltophilia* are uncommon. *Pat* gene source which is *Streptomyces viridochromogenes* strain Tu 494, is a gram-positive spore-forming soil bacterium which produces bialafos (phosphinothricin), a tripeptide composed of two molecules of L-alanine and an analog of L-glutamine acid. *Agrobacterium sp*. strain CP4 as well as other bacteria and some soul fungi, are resistant to the action of glyphosate for possessing the EPSPS enzyme. All plant, microbial, and fungal food sources contain EPSPS proteins, therefore, this enzyme and its activity are not novel to the food supply. *Sphingobium herbicidovorans* is a gram-negative soil bacterium that is widespread in the environment and naturally produces the novel AAD-1 protein. Living organisms are therefore regularly exposed to *S. herbicidovorans* and its components, without known adverse consequences [69].

3. Compositional analyses were conducted on grain and forage harvested from MON 87429 and the conventional control grown in the United States during the 2017 season. Samples for this study were harvested from five sites. The evaluation of MON 87429 followed considerations relevant to the compositional quality of maize as defined by the OECD consensus document. Compositional data confirmed that forage and grain from MON 87429 are compositionally equivalent to conventional maize, and therefore the food and feed safety and nutritional quality of this product is comparable to that of the conventional maize [3][70].

4. MON 87429 was not found in the GM Approval Database of ISAAA.

5. CFIA and Health Canada have received a submission from Monsanto Canada ULC seeking an environmental safety approval for commercial planting purposes and livestock feed and food use of a maize line designated as MON 87429, which has been genetically modified to exhibit herbicide tolerance. The submission received is in accordance with CFIA guidelines for assessment of plants with novel traits for unconfined release, CFIA guidelines for assessment of novel feeds from plants with novel traits, and Health Canada guidelines for assessment of novel foods.

6. Canadian civil society groups, the Canadian Biotechnology Action Network (CBAN) and Prevent Cancer Now (PCN) call for a review of the use of genetically engineered or genetically-modified or GM herbicide-tolerant crops in Canada, in response to Monsanto's request for government approval of a GM corn that can withstand applications of four herbicides, including 2,4-D and dicamba [71].

Based on the evaluation of available literature and dossier documents presented, MON87429 applied for Direct Use as Food, Feed or for Processing (FFP) is safe as its conventional counterpart except for its herbicide tolerance and hybridization traits. Use of this event in its usual context is not expected to pose any new or additional risk to human health.

DENR-BC'S ASSESSMENT AND CONSLUSION

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 for food, feed, or for processing of Corn MOR874R9, the DENR-BC considered that the regulated article poses no significant adverse effect to the environment on the following bases:

1. The host plant is widely grown and is known for its history of domestication and safe use as the third leading whole grain crop. Most corn plants grown at the present are hybrids that have been derived from crossbreeding, which has a history of safe use. The regulated article has also been approved for unconfined release and direct use in Canada [1][57][58][59].;

2. The inserted genes in the regulated article and have all been previously assessed. The genes were also stably introduced, the expressed proteins have no sequence or structural similarities to any known toxin and would be completely degraded before being absorbed in the gastrointestinal tract [1][57][58][59].;

3. The overall compositional analyses support that the regulated article and the conventional and commercially available corn grains are equivalent in composition, except for the intended modifications [1][57][58][59].;

4. There is a low likelihood that the regulated article will become weedy or invasive in unmanaged and uncultivated habitats since maize cannot grow in wild, non-agricultural environments such as roadsides [1][57][58][59].; and

5. The Project Description Report (PDR) discusses the specified environmental management plan indicating the possible risk and harm to the environment particularly on biodiversity, as well as the mitigating measures and contingency plan [1][57][58][59].

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

SEC EXPERT'S ASSESSMENT AND RECOMMENDATION

Corn is the preferred feed-grain by local end-users although due to concerns related to quality (i.e., aflatoxin) from locally produced corn, most feed-mills have preferred imported corn for its reliability and uniformity. In response to local feed requirements, the domestic feed milling industry continues to consolidate and modernize to meet the feed needs of the growing livestock and poultry industries.

In May 19/20, feed-corn demand will increase to 6.7 million tons as prices abate, while food consumption will decline to two million tons. The common feed ingredients used in the Philippines include corn, rice bran, copra meal, feed-wheat, cassava, soybean meal, fish meal, coconut oil, salt, and assorted vitamins and minerals.

To discourage corn price surges, large feed mills enter into supply agreements with local corn and cassava producers in exchange for assured prices and technical assistance.

The analysis and verification of the data provided shows the importance of importation to meet the requirements of the animal industry. This is reflected by the self-sufficiency ratio which has declined from 93.12% in 2014 to 88.43% in 2018. This indicates the growing dependency on corn importation to meet the growing requirements of the animal industry for corn.

Given the information provided, the SEC expert agrees with the applicant that there will be no significant effect of importation of the GM corn on the production, consumption/utilization and trade given the trade deficit in pork, broiler and eggs.

There is no possible effect on the cultural practices because the imported GM material is intended only for food and feed and/or processing and not for production.[63][64][65][66][67].

Recommendation

The SEC expert recommend for the approval and issuance of the biosafety permit of the GM product.

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