

ASSESSORS' CONSOLIDATED REPORT ON MONSANTO PHILIPPINES INC'S CORN MON 87460 FOR DIRECT USE AS FOOD AND FEED, OR FOR PROCESSING

EXECUTIVE SUMMARY

On August 2, 2017, Monsanto Philippines Inc. submitted corn MON 87460 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 applicant, 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 corn MON 87460 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 event provided 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 corn MON 87460 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 corn MON 87460.

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 Syngenta 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 Syngenta Philippines Inc. 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 EVENTS

MON 87460 expresses a cold shock protein B (CSPB) produced from the *Bacillus subtilis*-derived gene inserted into corn using *Agrobacterium*-mediated transformation system. It also expresses the neomycin phosphotransferase II (NPTII) from *Escherichia coli*, as selectable marker that confers tolerance to antibiotics such as neomycin and kanamycin. MON 87460 reduces yield loss under water-limited conditions.

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

| Country | Food direct use or processing | Feed direct use or processing | Cultivation domestic or non-domestic use |
|----------------|--------------------------------------|--------------------------------------|---|
| Australia | 2010 | | |
| Brazil | 2016 | 2016 | |
| Canada | 2011 | 2010 | 2010 |
| China | 2013 | 2013 | |
| Colombia | 2011 | 2012 | |
| European Union | 2015 | 2015 | |
| Indonesia | 2017 | | |
| Japan | 2011 | 2011 | 2012 |
| Mexico | 2011 | | |
| New Zealand | 2010 | | |
| Nigeria | 2018 | 2018 | |
| Philippines | 2012 | 2012 | |
| Singapore | 2015 | 2015 | |
| South Korea | 2012 | 2011 | |
| Taiwan | 2011 | | |
| Thailand | 2013 | | |
| Turkey | | 2017 | |
| United States | 2010 | 2010 | 2011 |
| Vietnam | 2015 | 2015 | |

Source: <https://www.isaaa.org/gmapprovaldatabase/event/default.asp?EventID=98>

STRP's Assessment

1. Host Organism

- a. Corn is a source of carbohydrates, macronutrients, vitamins, and minerals. It is also a significant source of sulfur-containing amino acids methionine and cystine, and antioxidants like vitamins A and E [1][2][3][4].
- b. Maize or corn does not contain significant toxicants and is not a common allergenic food. It has been used for centuries as a staple food and is primarily utilized in the production of animal feed [1][2][5].

2. Donor Organism

- a. The donor organisms are: *Bacillus subtilis* and *Escherichia coli*, which are not known to possess toxicogenic or allergenic property in humans or animals, and have a long-standing history of safe use in crop genetic improvement through recombinant DNA technology [6][7][8][9][10].
- b. The *cspB* gene (source of the CSPB protein) which codes for water tolerance was derived from *B. subtilis*; while the *nptII* gene (source of NPTII protein) which confers antibiotic resistance was taken from *E. coli* [11][12][13][14][15][16][17][18][19][20][21][22][23].
- c. The safety assessments of the CSPB and NPTII proteins and their donor microorganisms demonstrate safe use for human consumption [11][24].

3. Transformation System

- a. The PV-ZMAP 595 plasmid vector was used in the development of the transgenic MON87460 through *Agrobacterium*-mediated transformation [11][25].
- b. The target of genetic modification is the nuclear DNA. An intact copy of the *cspB* and *nptII* expression cassette was integrated at a single chromosomal locus of the genome of MON87460 [25][26].

4. Food and Feed Safety

- a. The digestibility of CSPB and NPTII were demonstrated using SDS-PAGE and Western Blot analysis. Results indicated that both proteins are digestible using simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) with pepsin and pancreatin as the main digesting enzymes, respectively. [25][26][27][28].
- b. The CSPB protein is functionally inactivated and degraded by heat treatment. The ELISA detection assay demonstrated the inactivation of the CSPB protein at 204°C after 15 minutes of exposure. Meanwhile, no heat inactivation study was performed for the NPTII protein since it has a very low level of expression in the MON87460 corn grain [6][26].

- c. The CSPB and NPTII have no significant homology with known toxins. The bioinformatics analyses of CSPB and NPTII protein sequences using FASTA sequence alignment demonstrated no similarities with protein and toxin sequences in databases [26][29][30][31].
- d. Acute oral toxicity studies were performed for both CSPB and NPTII proteins. There were no observable adverse effects on mice even at acute oral gavage of 4.7 mg/kg of body weight and 5000 mg/kg of body weight for CSPB and NPTII, respectively [11][26][28].
- e. The CSPB and the NPTII proteins are independently expressed and each has a functional activity in the transgenic MON87460 corn. The CSPB protein is expressed within the organelle while NPTII was used as a detectable marker [11][26][32][33].
- f. The CSPB and NPTII proteins have no significant homology with known allergens. The bioinformatics analyses of CSPB and NPTII protein sequences using FASTA sequence alignment demonstrated no similarities with allergen sequences in databases [26][29][30][31].
- g. There is a statistically significant difference in the moisture and fat composition of MON87460 and the conventional untransformed counterpart, but these levels of difference are well within the confidence interval of 99% [35][36][37].
- h. There is no statistically significant difference in the proximate analysis of MON87460 and the commercial counterpart varieties. The subtle differences are well within the confidence interval of 99% [35][36].
- i. There is a statistically significant difference in the fatty acid composition of MON87460 and the conventional untransformed counterpart as well as the conventional commercial counterpart, but these levels of difference are well within the confidence interval of 99%. The observed slight differences in magnesium, carbohydrates, calcium and some fatty acids were not considered biologically meaningful [35][36][37][38].
- j. There is no statistically significant difference in the key nutrient analysis of MON87460 compared to the conventional untransformed counterpart and the commercial counterpart varieties. The subtle differences are well within the confidence interval of 99% [35][36].

STRP's Conclusion

After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines, Inc. relevant to Corn MON 87460, the STRP found 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 any significant risk to human and animal health.

Furthermore, the STRP found that the new studies submitted by the applicant will not affect the safety of Corn MON 87460 [56][57][58][59][60][61].

BAI's Assessment

1. Toxicological Assessment

- a. The enzymes used for the digestibility study of CSPB protein were pepsin and pancreatin. The SDS-PAGE and Western Blot analysis indicated that the CSPB protein was digested within 30 seconds of digestion [27][39].
- b. The SGF and SIF were used to assess the susceptibility of the NPTII protein. Results indicated that the protein was degraded at 10 seconds in SGF, while 50% degradation occurred after 2 to 5 minutes in SIF [28][41].
- c. The heat inactivation study for the CSPB protein was assessed using ELISA. The estimated T_{50} after heat inactivation was 15 minutes at 204°C [11][42].
- d. The CSPB protein sequence shares identity to other naturally occurring CSD-containing proteins found in food and food products [29][31].
- e. The NPTII protein sequence shows no biologically relevant sequence similarities to allergens or toxins in databases [44].
- f. Acute oral toxicity studies were performed for both CSPB and NPTII protein. The No Observed Adverse Effect Level (NOAEL) were 4.7 mg/kg body weight and 5000 mg/kg body weight for the CSPB and NPTII proteins, respectively [28][45][46].
- g. The CSPB protein is distributed in both cytoplasm and nuclei while the NPTII protein is expressed independently and functions only as a selectable marker [33][47].

2. Allergenicity Assessment

- a. The CSPB and NPTII proteins have no meaningful sequence similarities to known allergens and toxins from all the databases as demonstrated in the bioinformatics analyses [44][51].
- b. The mean level of CSPB in MON87460 grain is 0.072 µg/g (dw), mean percent dry weight of total protein is 10.50% (105,000 µg/g), and percent corn grain protein is 0.00007% [53].
- c. The total NPTII protein in MON 87460 grain is 9.46% (94,600 µg/g) fresh weight, percent of protein in corn grain is 0.000005% (fw), and 0.000006% of total corn grain protein (dw) [40].

3. Nutritional Data

- a. For the proximate analysis of the CSPB and NPTII protein (total fat and moisture for grain and forage), the significant differences observed were within the 99% tolerance interval established from the commercial reference [34][35].

- b. There were significant differences in the proximate analysis of CSPB and NPTII protein (key nutrients) but none of the differences were biologically meaningful and were within the 99% tolerance interval [35][36].

BAI's Conclusions

After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines, Inc. relevant to Corn MON 87460, BAI found scientific evidence that the regulated article applied for direct use has no evidence of interaction on the resulting gene products.

Furthermore, BAI agrees with the applicant's claim that the gene modification will not affect the safety of CORN MON87460 as supported by the new studies submitted by the applicant.

There were six (6) new relevant studies provided by the applicant which spanned from 2014 to 2015. Results of the identified studies showed lack of any nutritional and compositional issues attributable to the inserted trait which suggests the safety of MON87460. [56][57][58][59][60][61].

BPI-PPSSD'S ASSESSMENT

1. Toxicological Assessment

- a. The CSPB and NPTII protein were rapidly degraded in simulated gastric fluid (SGF) containing pepsin within 30 seconds and 10 seconds, respectively, as demonstrated in the SDS-PAGE and Western Blot assays [26][27][28].
- b. The ELISA analysis of the CSPB protein indicated that 91% loss in immunodetectable level was observed upon incubation at 204°C for 15 minutes [11][26].
- c. For the NPTII protein, heat stability study was not conducted since the level of protein expression in MON 87460 grain was below the LOQ [43].
- d. The results of bioinformatics analysis using FASTA sequence alignment showed that CSPB and NPTII proteins have no homology to any known toxins and allergens in the database [26][31][44].
- e. The acute oral toxicity studies of CSPB and NPTII proteins administered by gavage to mice at dose of 4.7 mg/kg and 5000 mg/kg body weight demonstrated no treatment-related effects on survival, clinical observations, body weight gain, food consumption or gross pathology [26][28][45].
- f. The CSPB protein is distributed in both cytoplasm and nuclei, and was previously observed in corn protoplasts; while the NPTII protein functions only as a selectable marker [33].
- g. The CSPB and NPTII proteins have distinct modes of action and there is no interaction among these proteins that could lead to adverse effects in humans, animals or environment [50].

2. Allergenicity Assessment

- a. The bioinformatics analyses of CSPB and NPTII proteins using FASTA sequence alignment showed that both proteins have no homology to any known allergen and toxins in the databases [30][31][44][51][52].
- b. The percent of CSPB protein in one gram of MON87460 grain is 0.00007%, while the NPTII protein is 0.000005% which both indicate a very low concentration of CSPB and NPTII proteins in MON87460 corn grain [40][53].

3. Nutritional Data

- a. The statistically significant differences (total fat in grains, total fat and moisture in forage, key nutrients) in the proximate analysis of MON87460 were within the 99% tolerance interval established from the commercial references and are not considered biologically relevant [34][35][36].

BPI PPSSD's Conclusions

For the single event, MON 87460 corn, enough evidences were considered to support the substantial equivalence of the genetically modified crop in terms of nutritional composition and food safety, with the conventional corn other than the reduction of yield loss under water-limited conditions and tolerance to certain antibiotics. After reviewing the provided material of Monsanto Philippines, Inc. and other literature, it is therefore concluded that MON 87460 corn is as safe as its conventional counterpart.

After a thorough review of the new studies submitted by Monsanto Philippines, Inc. for MON 87460 application for direct use as food, feed and fo processing, the BPI-PPSSD-FSRAT found that the new studies submitted by the applicant will not affect the safety of MON 87460 corn.

Wang et al. [56] characterized and assessed the safety of the introduced shock protein B (CSPB) in DroughtGard™ maize. The purification and characterization of CSPB protein through N-terminal sequence analysis, peptide mass mapping, SDS-PAGE analysis, functional activity assay and glycosylation analysis established the equivalence of the plant-produced and *E. coli*- produced CSPB. The safety of CSPB protein was demonstrated through digestibility studies, amino acid sequence comparison and acute oral toxicity study. Results of the analyses indicated that CPSB protein is not toxic or allergenic.

Venkatesh et al. [57] compared the composition of near-isogenic GM, MON 87460, NK603 and MON 89034 and conventional maize hybrids. The statistical analysis yielded no biological differences between the composition of MON 87460 and the conventional maize. This is comparable to the findings of Xu et al. [58] who also compared MON 87460 to conventional maize using univariate and multivariate assessments.

DOH-BC's Assessment

The DOH BC found 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. Scientific pieces 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 as safe as food or feed derived from conventional corn varieties.

DOH-BC's Conclusion

After a thorough scientific review of technical documents regarding new studies conducted on CORN MON87460 and submitted by Monsanto Philippines Inc. applied for direct use as Food and Feed or for Processing, the DOH Biosafety committee agrees with the applicant's claim that the gene modification will not affect the safety of CORN MON87460 as supported by the new studies submitted by the applicant. [56][57][58][59][60][61].

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.

ANNEX V

DENR-BC's Assessment

After a thorough and scientific review and evaluation of the documents provided by the Bureau of Plant Industry (BPI) on the application of Monsanto Philippines, Inc. for Direct Use as Food and Feed or the Processing of Corn MON87460, here under are the observations and appropriate actions:

1. From the evaluation of the application submitted by the proponent, including the scientific evidences provided, references and literature, as well as other related studies, the Committee finds that the direct use of the regulated article whether for food, feed and/or the processing will not cause any significant adverse effect on the environment (land, air, and water) and non-target organisms, to wit.

- a) Genetic stability in the transgenic crop is ensured such that no unintended horizontal gene transfer shall occur to unrelated species
- b) The protein product produced by the transgenic crop will degrade upon exposure to the natural environment and general conditions (i.e. high temperatures (60 C and above), varying pH, enzyme digestion, etc.); and
- c) The protein product will not increase the weediness potential of the transgenic crop.

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

2. The project description report (PDR) discusses the specified environmental management plan indicating the possible risk and harm to the environment and non-target organisms as well as the mitigating measures and contingency plan of the proponent. Upon evaluation of the submitted PDR and environmental risk assessment (ERA), the Committee notes that the chances of unintended release or planting of the regulated article is very minimal and will not cause any damaging and lasting effects because the receiving environment (areas near the port, roads, railways, etc.) is not conducive for plant growth/germination.

3. The Bureau of Plant Industry (BPI) shall ensure the proper and secure packaging of the regulated article for transport and the safety and durability, of the transport, vehicle, for prevention of any possible spillage or unintended release during transport/import as per BPI's inspection in the port area.

DENR-BC's Conclusion

The DENR-BC found scientific evidence that the regulated article applied for direct use as food and feed or processing is safe as its conventional counterpart and is not expected to pose any significant risk to the environment and to non-target organisms. Based on the above considerations and with the proponent's sworn statement of accountability, we hereby submit our evaluation relative to Monsanto Philippines, Inc. MON87460 application for biosafety permit for food, feed, and for processing.

The new studies submitted have been acknowledged by the DENR-Biosafety Committee. [56][57][58][59][60][61].

SEC Expert's Assessment

1. GM corn is widely produced and consumed, and is a significant component of global trade of agricultural commodities. In 2014, the Bureau of Plant Industry reported an aggregated GM Corn adoption of 707,003 hectares by almost half million Filipino farmers [54].
2. The approval of Corn MON87460 will not drastically affect the current patterns of production, consumption/utilization and trade [55].
3. Corn MON87460 is not expected to influence the consumption pattern of the consumers of poultry and livestock products [55].

4. Corn MON87460 will help improve the global trade and increasing local production will help improve our competitiveness in corn production and will result to more money/income/pesos for the country which can be used for various projects [55].

SEC Expert's Recommendation

The impact of GM Corn MON 87460 to the feed industry and ultimately to the livestock, poultry and the aquaculture sub-sectors would be tremendous. Increased local production of yellow corn will help save millions for our country.

With the above scenario and observed consequences of Corn MON 87460, the SEC Expert recommends the renewal of permit of the MON 87460. The renewal of the utilization of GM corn would help the feed industry and may result in lower production cost of poultry, livestock and aquaculture products in our country. However, concerned agencies, both government and non-government, should continue to monitor and regularly assess the risk of any GM products introduced in the country.

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