

**ASSESSORS' CONSOLIDATED REPORT ON MONSANTO PHILIPPINES INC'S
CANOLA MON88302 APPLICATION FOR DIRECT USE AS FOOD, FEED OR FOR
PROCESSING**

EXECUTIVE SUMMARY

On April 29, 2019, Monsanto Philippines Inc. filed for application of canola MON88302 for direct use as food and feed, or for processing, as original application under the DOST-DA-DENR-DOH-DILG Joint Department Circular (JDC) No. 1 Series of 2016. After reviewing the Risk Assessment Report and attachments submitted by the Monsanto Philippines Inc., the assessors namely: Scientific and Technical Review Panel (STRP), BPI Plant Products Safety Services Division (BPI-PPSSD) and Bureau of Animal Industry-Biotech Team (BAI-BT), concurred that canola MON88302 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 canola MON88302, provided that the conditions set by DENR are complied. Also, the Department of Health – Biosafety Committee (DOH-BC), after a thorough scientific review and evaluation of documents related to Environmental Health Impact, concluded that canola MON88302 will not pose any significant risk to the health and environment and that any hazards could be managed by the measures set by the department. DOH-BC also recommended for the issuance of biosafety permit for the transformation canola MON88302.

Furthermore, the Socio-economic, Ethical and Cultural (SEC) Considerations expert also recommended for the issuance of biosafety permit for this regulated article after assessing the socio-economic, social and ethical indicators for the adoption of Genetically Modified Organisms.

Background

In accordance with Article VII. Section 20 of the JDC, no regulated article, whether imported or developed domestically, shall be permitted for direct use as food and feed, or for processing, unless: (1) the Biosafety Permit for Direct Use has been issued by the BPI; (2) in the case of imported regulated article, the regulated article has been authorized for commercial distribution as food and feed in the country of origin; and (3) regardless of the intended use, the regulated article does not pose greater risks to biodiversity, human and animal health than its conventional counterpart.

The BPI Biotech Office provided the assessors the complete dossier submitted by Monsanto Philippines Inc. The SEC expert, on the other hand, was provided with a questionnaire on socio-economic, ethical and cultural considerations that have been addressed by canola MON88302 in relation to their application. These assessors were given thirty (30) days to submit their independent assessment to BPI Biotech Secretariat.

INFORMATION ON THE APPLIED EVENT

Monsanto Company has developed a second-generation glyphosate-tolerant canola product, MON 88302, designed to provide growers with improved weed control through tolerance to higher rates of glyphosate and greater flexibility for glyphosate herbicide application. Canola MON 88302 contains a cp4 epsps coding sequence derived from *Agrobacterium* sp. strain CP4 that expresses 5-enolpyruvylshikimate-3-phosphate synthase (CP4 EPSPS) protein. The CP4 EPSPS protein confers tolerance to the herbicide glyphosate, the active ingredient in Roundup® brand of agricultural herbicides. MON 88302 was developed through *Agrobacterium*-mediated transformation method.

**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	2012	2012	2014
Canada	2012	2012	2012
China	2018 *	2018 *	
European Union	2015	2015	
Japan	2013	2013	2013
Mexico	2013		
New Zealand	2012	2012	
Philippines	2015	2015	
Singapore	2017		
South Korea		2014	
United States	2012	2012	2013

Source: <https://www.isaaa.org/gmapprovaldatabase/event/default.asp?EventID=255> Last updated: May 16, 2019

STRP's Assessment

1. Host Organism

- a. Canola is a known source of key nutrients containing about 40% oil and 23% protein and is used for food and feed.[1][2][4][4].
- b. Antinutrients such as glucosinolates, sinapine, phytic acids and tannins are present in canola. Glucosinolates are natural components of many pungent plants such as mustard, cabbage, and horseradish. Sinapine is an alkaloidal amine found in some seeds, particularly oil seeds of plants in the family Brassicaceae. It is the choline ester of sinapic acid. Phytic acid is the phosphate ester of inositol. It has a significant nutritional role as the principal storage form of phosphorus in many plant tissues, especially bran and seeds. Tannins (or tannoids) are a class of astringent, polyphenolic biomolecules that bind to and precipitate proteins and various other organic compounds including amino acids and alkaloids.[5].
- c. Canola contains toxicants such as glucosinolates and erucic acid. Myocardial lipidosis and heart lesions in laboratory rats was the effect of erucic acid. This would be particularly so if the level of erucic acid in canola oil were to exceed 2% of the total fatty acids.[6][7][8][9][10].
- d. There have been no allergenic reaction reported for canola oil, hypersensitivity is relatively very low in occurrence compared to common plant allergens.[1][14][15][16].
- e. Canola is grown and consumed principally as vegetable oil. Canola oil is the third world's largest source of vegetable oil. Consumption is at 15% after soybean oils at 28% and palm oil at 32%. [1][11][12][13].
- f. Canola oil together with coconut, soybean and other oils comprise about 20% of the domestic oil requirements. It is also used as feed, in the form of canola meal for swine, poultry and in fish feed. [16][17][18][19][20][21][22].

2. Donor Organism

The *Agrobacterium sp.* strain CP4, which was used as the donor organism, has a history of safe use and is not known or reported to have similar sequences to any known protein that cause allergenicity or toxic effect in livestock, poultry and man to date. It is also present in very negligible amounts in canola oil. [1][23][24][25][26][27].

3. Transformation System

- a. Canola MON 88302 was developed by *Agrobacterium tumefaciens*-mediated transformation with genomic DNA being the target of modification. It expresses 5-enolpyruvyl-shikimate-3-phosphate synthase (EPSPS) from *Agrobacterium sp.* strain CP4, which confers tolerance to the herbicidal active substance glyphosate.[28][29].
- b. The *cp4 epsps* was the only expressible gene sequence, the expressed protein has no reported case of allergenicity or toxicity. CP4 EPSPS protein is widely utilized to

develop transgenic herbicide locally and internationally. [1][28][34][39][40][42][46][47][48].

- c. Canola MON 88302 was produced using plasmid vector PV-BNHT2672 that contains the one transfer DNA (T-DNA). Hypocotyl segments were excised from dark grown seedlings of germinated canola seed. After co-culturing with the *Agrobacterium* carrying the vector, the hypocotyl segments were placed on medium for callus growth containing carbenicillin, ticarcillin disodium and clavulanate potassium to inhibit the growth of excess *Agrobacterium*. The hypocotyls were then placed in selection media containing glyphosate to inhibit the growth of untransformed cells and plant growth regulators conducive to shoot regeneration. Rooted plants with normal phenotypic characteristics were selected and transferred to soil for growth and further assessment.[1][30][31][32][33][34][35][36][37][38][39].

4. Food and Feed Safety

- a. The expressed protein CP4 EPSPS (5-nolpyruvylshikimate-3-phosphate synthase from *Agrobacterium* sp. strain) was assessed for digestibility. Results show that CP4 EPSPS is digestible. SDS PAGE followed by Western blot analysis demonstrated that more than 95% of the CP4 EPSPS protein was degraded at below 15 seconds and the novel protein was almost completely digested. Hence, expected allergenicity of this protein is extremely low.[1][23].
- b. Studies on the temperature dependent study revealed that enzymatic activity of EPSPS is eliminated at 65°C incubation for 15 minutes. This shows that the protein is functionally inactivated by heat. However, the SDS-PAGE demonstrated that heat treatment even at 95°C for 15-30 minutes is indeed functionally inactivated but the structural integrity of the protein is not affected. This implies a possibility that denaturation may be reversible.[1][40][41].
- c. The calculated proportion of the CP4 EPSPS protein is indeed very small relative to the total protein harvested in canola seeds. No significant sequence similarities between CP4 EPSPS and known allergens, toxins and gliadins were identified using the FASTA alignment tool. Also, EPSPS is an enzyme present in many foods and is not expected to cause toxicity and allergenicity.[1][26][42][43][44][45][46].
- d. An acute mouse gavage study demonstrated that the CP4 EPSPS is not toxic. No treatment related adverse effects were observed in animals administered CP4 EPSPS protein by oral gavage at doses up to 572 mg/kg body weight, this is 1000-fold of the anticipated consumption level.[23][58].
- e. The shikimate pathway and, hence, EPSPS proteins, are absent in mammals, fish, birds, reptiles and insects. It has been estimated that aromatic molecules, all of which are derived from shikimic acid, represent 35% or more of the dry weight of a plant.[59].
- f. The protein, CP4 EPSPS, encoded by the expressible inserted sequence, is indeed not toxic nor is an allergen. This is also due to the fact that CP4 EPSPS is widely utilized to develop transgenic herbicide tolerant plants and has a long-standing history of safe use, both locally and internationally.[60].

STRP's Conclusion

After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines, Inc., relevant to canola MON 88302, 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.

BAI's Assessment

1. Toxicological Assessment

- a. The source of test protein used in the toxicological assessment was *E. coli*-produced CP4-EPSPS which is proven to be equivalent to the plant-produced CP4-EPSPS present in MON 88302.[1][47]
- b. The *E. coli* –produced CP4-EPSPS protein was subjected to Simulated Gastric Fluid (SGF) using pepsin as enzyme and was analyzed using SDS-PAGE and Western blot methods. Results have shown that greater than 98% of the protein was digested within 15 seconds while the Western blot analysis showed that greater than 95% of the *E. coli*-produced CP4 EPSPS protein was digested within 15 seconds.[1][40].
- c. The estimated T₅₀ result after heat treatment of CP4 EPSPS protein is below 15 minutes. This result is based on a functional activity assay and SDS-PAGE. The functional activity is below the Limit of Detection (LOD) of the assay when incubated at 75 °C or higher for either 15 or 30 minutes while the SDS-PAGE showed that there is no significant change in band intensity of the heat-treated samples after incubation for 15 or 30 minutes at all temperatures tested.[1][76].
- d. Alignment using the FASTA showed that there is no structurally relevant similarity present between CP4 EPSPS protein and known toxins.[1][40].
- e. Acute oral mouse toxicity study was conducted to evaluate the toxicity of the CP4 EPSPS protein. The considered No Observable Adverse Effect Level (NOAEL) was 572 mg/kg which was the highest dose tested.[1][23][48].

2. Allergenicity Assessment

- a. The source of test protein used in the toxicological assessment was *E. coli*-produced CP4-EPSPS which is proven to be equivalent to the plant-produced CP4-EPSPS present in MON 88302.[1][47].
- b. The digestibility assessment concludes that the T₅₀ result for SGF of CP4 EPSPS is below 15 seconds. After digestion, no fragments remained and during heat treatment, functional activity was lost, while no change in the band intensity in the samples was observed.[1][47].
- c. Bioinformatics analyses were performed to assess the potential for allergenicity of the CP4 EPSPS protein sequence using FASTA and ALLERGENSEARCH. The analyses showed that there is no alignment between CP4 EPSPS to any known allergens.[1][40][47][49].

3. Nutritional Data

- a. There was no statistically significant difference observed in antinutrients, ash, carbohydrates by calculation, moisture, protein, and total fat between MON 88302 and conventional canola.[1][50].
- a. The components with statistically significant differences are total dietary fiber and seven fatty acids which are 16:1 palmitoleic acid, 18:0 stearic acid, 18:1 oleic acid, 18:2 linoleic acid, 18:3 linolenic acid, 20:0 arachidic acid, and 22:0 behenic acid. The differences observed were small relative to the natural variability of the components as determined by the 99% tolerance interval according to literature values.[1][50].

BAI's Conclusion

After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines, Inc. relevant to canola MON 88302, 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 and Allergenicity Assessment

- a. SDS PAGE and Western Blot showed that CP4 EPSPS protein was rapidly digested in SGF within 15 seconds. Heat inactivation assay using SDS PAGE showed that the functional activity of CP4 EPSPS was below the LOD when incubated at 75 °C or higher for either 15 or 30 minutes, but without significant change in band intensity of the heat-treated samples.[40][49].
- b. Bioinformatics analysis using the full-length sequence, an 80-mer sliding window and 8-mer exact match did not yield significant homology of CP4 EPSPS to any known allergen and toxins.[91][64].
- c. Digestibility, heat inactivation, amino acid sequence comparison and oral toxicity studies, indicated that the novel protein CP4 EPSPS is digested rapidly in mammalian gastric fluid. Dietary proteins are inactivated by induction of heat which is normally occurring during processing and cooking. Acute oral gavage of CP4 EPSPS was performed and did not cause toxicity on mice. [40][49][51][52].

2. Nutritional Data

- a. Compositional analysis indicated no significant difference between the antinutrients, ash, carbohydrates by calculation, moisture, protein, total fat levels fiber, amino acid, fatty acid, vitamin E and mineral content of MON 88302 and the conventional control. All test values of proximates were within or similar to literature and historical values. [50]

- b. Statistical difference was noted for the total dietary fiber (TDF), palmitoleic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, arachidic acid and behenic acid.[50].

BPI PPSSD's Conclusion

After thorough evaluation of the documents provided by the proponent and scientific literature search conducted and other literature, the BPI-PPSSD concludes that the weight of evidence's approach indicates that canola MON 88302 is as safe as its conventional counterpart with regards to substantial equivalence and food safety.

DENR-BC's Assessment

- a. 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) particularly on biodiversity. The CP4 EPSPS protein product produced by the transgenic crop will degrade upon exposure to the natural environment and general conditions at high temperatures (65°C and above), varying pH, enzyme digestion.[52][53];
- b. The donor organism for CP4 EPSPS protein, *Agrobacterium* sp. is ubiquitous to the environment and does not pose significant risk of pathogenicity to animals. Bioinformatics analysis showed that CP4 EPSPS has no structural similarity to any putative toxins to mammals [54]; and
- c. 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. Furthermore, the chances of unintended release or planting of the regulated article is 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. Also, canola is sensitive to weather changes, early growing conditions, and seedbed conditions thus need human intervention.[55].

DENR-BC's Conclusion

After a comprehensive review and evaluation of the documents including the scientific evidence from references and literature submitted by Monsanto Philippines, Inc., on its application for Direct Use as FFP of Canola MON88302, DENR-BC considered the regulated article safe to the environment particularly on biodiversity. [113][114][115].

DOH-BC's Assessment

- a. 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.
- b. Dietary exposure to the regulated article is unlikely to result in allergic reaction.
- c. The regulated article is as safe as food or feed derived from conventional canola varieties.
- d. The regulated article is not materially different in nutritional composition from that of the non-transgenic canola or the conventional canola.

DOH-BC's Conclusion

After a thorough review and evaluation of the documents provided by the proponent Monsanto Philippines, Inc. in support of their application for approval of direct use as food, feed or for processing (FFP) of canola MON 88302, 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.

DOH-BC' 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

- a. Canola is not being cultivated in the Philippines. It is imported and consumed mainly in the form of cooking oil.[56].
- b. Canola oil consumption in the Philippines accounts for less than one percent of the total oil consumption. However, there is an expected surge in the value of the cooking oil market due to the growth of the food manufacturing industry.[56].
- c. Preference for canola oil is being observed as it is popular for its nutritional qualities and low saturated fats. Canola GM products will not drastically change current patterns of production, consumption/utilization and affect specific and cultural groups but will help to maintain global trade of canola products that are imported into the Philippines and ensure food security for increasing food demand.[57].

SEC Expert's Recommendation

After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines Inc., relevant to canola MON 88302, the SEC expert recommended for the approval and issuance of biosafety permit of the said GM product.

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