ASSESSORS' CONSOLIDATED REPORT ON MONSANTO PHILIPPINES INC.'S CANOLA MON 94100 APPLICATION FOR DIRECT USE AS FOOD AND FEED, OR FOR PROCESSING

STRP's Assessment

1. Host Organism

a. Low erucic acid rapeseed seeds are processed into two major products: oil and meal. The canola oil is processed by crushing the grain and extracting the solvent to separate the oil from the meal. The oil is then used as oil dressing in salad, as cooking oil, and margarine, thereby consuming it as processed food product, not raw.[1][2][3][4][5].

b. The meal by-product from extracting the oil is used as a high protein feed source for all classes of livestock, poultry, and fish by mixing other feed items and additives.[1][2][3][6].

c. Canola's fatty acid profile contains key nutrients including palmitic, palmitoleic, stearic, oleic, linoleic, linolenic, galoleic (C20:1), eicosadienoic (C20:1), behenic (C22:0), erucic (C22:1) and lignoceric (C24:0) acids. Its oil is prized for its heart-healthy properties with the least saturated fat of all culinary oils.[2][7][8].

d. Canola also contains phytic acid, sinapine, and tannins as their anti-nutrient components.[2].

e. Canola contains erucic acid, a toxicant associated with cardiopathic potential in animal species which is detrimental to health if consumed in high amounts .[2].

f. Glucosinolates, a sulphur-containing component found in cruciferous plants are also toxicant found in canola. On their own, they are innocuous, but can come in contact with myrosinase enzyme resulting to the release of sulphur from hydrolyzing the glucosinolates when the seeds' cells are ruptured, reducing the palatability of canola meal.[2][3].

g. Canola hypersensitivity is relatively very low in occurrence compared to other common plant allergens such as pollens. Hypersensitivity associated with rapeseed flour inhalation especially to individuals allergic to mustard were also reported, however there is no conclusive proof for precautionary labeling of rapeseed as potentially dangerous for patients allergic to mustard.[9][10][11][12][13].

h. Food allergy to low erucic acid rapeseed oil has not been reported in scientific literature.[3].

i. In USA, canola represents 7 to 8% of total oil consumption, and is used in all food products requiring an oil source, while in the Philippines, Filipinos typically prefer coconut and palm oil except for individuals with higher incomes that perceive canola is a healthier alternative.[3][14].

2. Prior Safety Approval

MON 94100 was approved in Canada for food in 2021, it is considered to be as safe and as nutritious as its conventional counterpart and does not pose any risk to the environment. Furthermore, no change in consumption patterns will arise in introducing MON 94100 especially in light of the preference of Filipinos for coconut and palm oils.[1][15][16][17][18].

3. Donor Organism

a. The donor organism of the *dmo* gene is *Stenotrophomonas maltophilia* strain DI-6 which expresses the Dicamba Mono-Oxygenase (DMO) protein that confers tolerance to dicamba herbicide. Furthermore, the protein is not known to be toxic nor allergenic based on database search, *in vitro* digestibility, and *in vivo* tests.[1][19][20][21].

b. The *dmo* coding sequence in T-DNA I is under the regulation of the *PCISV* promoter, *TEV* leader sequence, the *RbcS (Ps)* chloroplast targeting sequence, and the *guf-Mt1* 3' untranslated region. The *aadA* and *splA* coding sequences in T-DNA II were also adequately described.[1][22][23][24][25][26][27][28][29][30][31][32][33][34].

c. The *S. maltophilia* is a ubiquitous microorganism that can be found in healthy individuals especially to those with reported pathogenicity and morbidity for severely immunocompromised/debilitated individuals. Despite its low susceptibility to several antimicrobials that cause infections and mortality of patients in hospitals, the *S. maltophilia* strains exert a range of biotechnological-relevant activities, such as bioremediation, degradation of toxic compounds, biosynthesis, and biological control in agriculture.[1][20][35][36][37][38][39][40][41][42][43].

d. DMO protein, which is also expressed in soybean MON 87708, cotton MON 88701, and corn MON 87419 using the same transformation system completed FDA consultation and is not known to be toxic or allergenic.[1][44][45][46][47].

4. Transformation System

a. The transformation method used is *Agrobacterium*-mediated transformation targeting the genomic DNA.[1][48].

b. Hypocotyl segments were excised from etiolated seedlings and were placed on carbenicillin-containing medium to inhibit the growth of excess *Agrobacterium* after co-culturing with the *Agrobacterium* carrying the plasmid vector. Transformants containing the selectable marker were selected and generated rooted shoots from the transformed callus tissues which were then evaluated by PCR. The transformed plants for the homozygous presence of the T-DNA I and absence of T-DNA II and vector backbone were then selected and evaluated for insert integrity using molecular analyses. The selected plants were then assessed if MON 94100 is the lead event and further evaluated its progeny in laboratory and field assessments.[48][49].

c. The transformation plasmid used (PV-BNHT508701) contains one T-DNA (with the *dmo* expression cassette) and the rest of the vector backbone containing the regulatory and intervening sequences are further detailed in Annex Table 1. No carrier DNA and/or helper plasmids were used.[1][26][50][22][23][24][25][26][27][28][29][30][31][32][33][34][51][52][53][53][55][56][57][58][59][60].

d. The plasmid vector is approximately 17.2 kb in length and contains two separate T-DNAs—T-DNA 1 (*dmo* expression cassette) and T-DNA II (*splA* and *aadA* expression cassettes). Traditional breeding, segregation analysis, selection, and screening were used to isolate plants containing only the *dmo* expression cassette after the transformation.[1][25][55][57].

e. Next Generation Sequencing (NGS) and mapping analyses were used in the molecular characterization of MON 94100. After undergoing Polymerase Chain Reaction (PCR), DNA sequence analyses were performed to determine the complete sequence of the insert and adjacent flanking DNA which confirmed that only a single copy of the T-DNA sequence is inserted in a single locus.[1][61].

f. The insert and flanking sequence were compared to the sequence of the insertion site in conventional canola and identified an 8 bp deletion at the site of insertion that occurred during integration of the T-DNA sequences. This anomaly is considered as a common 'side-effect' of transgenesis in the transformation event and has a very low chance of generating a novel chimeric Open Reading Frames (ORF) nor expressed polypeptite associated with it as demonstrated by bioinformatic analyses.[1][61][62][63][64].

g. Alignment was performed between the MON 94100 sequence and PV-BNHT508701 which confirmed the integrity of the organization and sequence of their genetic elements.[61].

h. DNA from five generations of seed tissues were used in NGS and bioinformatic analyses to confirm the multigenerational stability of the trait inserted in canola MON 94100. It was also confirmed that the inserted

gene was integrated and stably expressed in a single chromosomal locus that follows a Mendelian pattern.[1][61].

i. Enzyme linked immunosorbent assay (ELISA) was used to determine the expression levels of DMO protein and showed that the mean DMO protein was highest in roots and lowest in grain.[1][65].

5. Food and Feed Safety

a. DMO is digestible using Simulated Gastric Fluid (SGF) with pepsin as the main digesting enzyme. SDS-PAGE followed by Western blot analysis also demonstrated that more than 95% of DMO was degraded in 30 seconds. The protein, furthermore is functionally inactivated by heat.[66][67][68].

b. The expressed protein has no significant homology with known toxins as demonstrated by bioinformatic, chemical, biochemical, and molecular analyses which support the conclusion that food and feed products containing the DMO protein pose no meaningful risk to human or animal health. No mortality and test article-related clinical findings were also observed during the acute oral gavage study on mice of 140 mg/kg of body weight.[1][64][69][70][71][72].

c. MON 87708-produced DMO protein, an event that has been characterized and used for safety testing, was used as a reference substance in confirming the physico-chemical functional similarity of DMO produced in canola 94100 which ratified that both DMO produced proteins have the same amino acid sequences.[69].

d. The prevalence of the DMO protein is very small relative to the total protein harvested in canola seeds. Along with the very minimal consumption of DMO via refined canola oil, the potential risk of allergenicity from DMO in MON 94100 is greatly reduced.[1][3][65][69].

e. There was no statistically significant difference in the total proximates and key nutrients of MON 94100 and its conventional counterpart. Furthermore, the mean component values of MON 94100 were within the range of values observed in the literature and the ILSI-CCDB.[1][16].

f. MON 94100 contained a statistically higher concentration of sinapine, a minor anti-nutrient in canola seed, compared to SE comparator, however it was justified that the MON94100 was not a major contributor to variation in anti-nutrient levels in canola and confirmed the compositional equivalence of MON 94100 to the conventional control in levels of these components.[1][16].

g. Microwave treatment and soda ash treatment appears to reduce the concentration of sinapine, however the processing of canola seeds to produce food or feed products has no significance on the level of anti-

nutrients in addition to the further processing of the raw material that may lead to the destruction of the anti-nutrients.[1][16][73][74].

STRP's Conclusion

After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines, Inc. relevant to canola MON 94100, two of the STRPs found scientific evidence that the regulated article applied for Direct Use as Food and Feed or for Processing (FFP) is as safe and shall not pose greater risk to health and environment as its conventional counterpart. Furthermore, any risks posed to health and environment could be managed by the following measures:

a. Contracting of third-party to inform DA, make recommendations for proper storage, transport and distribution
b. Contracting of third-party to assess and monitor extent of any spills and make recommendations for containment

On the other hand, one of the STRPs did not recommend for the approval of canola MON 94100 due to the following reasons:

a. No other countries have approved canola MON 94100 for feed use, except Canada;

b. concerns on the use of *Stenotrophomonas maltophilia* due to its pathogenic nature; and

c. the increasing incidence of nosocomial and community-acquired *S. maltophilia* infections is of particular concern for immunocompromised individuals, as this bacterial pathogen is associated with a significant fatality/case ratio.[75].

BAI's Assessment

1. Toxicological and Allergenicity Assessment

a. Pepsin and pancreatin enzyme were used in the digestibility study with an estimated T_{50} for less than 30 seconds and less than 5 minutes respectively. Western blot analysis also confirmed that there was no large sized fragments observed during digestion.[66].

b. DMO activity assay confirmed that the resulting T_{50} was at 55°C both at 15 minutes and 30 minutes after heat treatment.[67].

c. No known toxins and allergens are similar to amino acid sequence of DMO as confirmed by bioinformatics analyses, with the DMO having an estimated molecular weight of 38.0 kDa without glycosylation sites as confirmed by glycosylation analysis. Furthermore, no mortality was

observed in acute oral gavage study performed in 10 mice wherein 140 mg/kg body weight was administered to each.[64][69][70][71][72].

d. The grain was emphasized in determining the protein levels in various parts of the plant as it is commonly used and processed as feed and was found out to have a computed DMO protein level of 0.64 µg/g dry weight.[1][3][65].

2. Nutritional Data

a. MON 94100 and the conventional control has no statistically significant differences ($p<0.05$) for proximate analysis, key nutrients in grain confirming the canola MON 94100 compositional equivalence to its conventional counterpart.[64][65][66][67][69].

b. MON 94100 demonstrated a statistically significant difference for sinapine with the conventional control but is within the literature values and ILSI-CCDB, thus is not biologically relevant.[1][16].

c. MON 94100 is compositionally comparable to conventional canola and is believed to not interact with any anti-nutrients found in canola. As a result, when MON 94100 and its progeny are used as a source of food or feed on a commercial basis, the products are unlikely to vary from equivalent meals or feeds derived from traditional canola.[64][65][66][67][69].

BAI's Conclusion

After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines, Inc. relevant to canola MON 94100, 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 analysis demonstrated the SGF and Simulated Intestinal Fluid (SIF) for the digestibility study of the DMO protein which indicated that it is readily digested in SGF within 0.5 seconds and in SIF within 5 minutes.[66].

b. DMO activity assay, as well as SDS-PAGE and Western blot analysis of the DMO protein tested the effects of heat in its activity at varying temperatures (0, 25, 37, 55, 75, and 95 °C) for 15 and 30 minutes. No drastic changes in the hybridization bands of DMO enzyme was observed

in SDS-PAGE upon treatment with heat for the same range and exposure.[67].

c. DMO in MON 94100 has no significant homology to any known toxin as confirmed using bioinformatic analysis (BLASTP and AllergenOnline), structural identity was also confirmed through N-terminal sequence/mass fingerprint and Western blot analysis. No glycosylation was confirmed as per glycosylation analysis, and molecular weight of 39.4 kDa for DMO+27, and 38 kDa for DMO was determined using Western blot analysis.[64][69].

d. The No Observed Effect Level (NOEL) of DMO protein based on acute oral gavage study is 140 mg/kg body weight and did not yield any treatment related effects on survival, clinical observations, body weight, food consumption and gross necropsy.[70]

e. The source of the test DMO protein is MON 87708 and was confirmed to be equivalent to MON 94100-produced DMO as per structural analysis, Western blot analysis, glycosylation analysis, and functional activity assay.[69]

f. The percent of DMO protein in MON 94100 grain is 0.00023% of the total protein based on the mean level of DMO protein in MON 94100 and the minimum percentage dry weight of total protein in the MON 94100 grains.[3][65].

2. Nutritional Data

a. No significant differences were observed between the proximate levels, amino acid, fatty acid, vitamin, mineral, fiber, anti-nutrient, and secondary metabolite of MON 94100 seeds and the conventional canola seeds except for the anti-nutrient sinapine which is higher than the conventional control but is not biologically relevant since the value is still within literature values range.[16].

b. All mean values for proximate analysis, key nutrients, and antinutrients were within the range of literature values.[16].

c. No significant differences were observed between the amino acid, fatty acid, vitamin, mineral, and fiber content of MON 94100 seeds and the conventional canola seeds based on compositional analysis.[16].

d. The effect of processing on the level of anti-nutrient and metabolites in MON 94100 seeds and the conventional control is expected to be similar.[1][16].

BPI PPSSD's Conclusion

After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines, Inc. relevant to canola MON 94100, PPSSD found scientific evidence that the regulated article applied for food is as safe as its conventional counterpart with regards to substantial equivalence and food safety.

DENR-BC's Assessment

a. Canola seeds are unlikely to persist if germination takes place. Seedlings that are in non-agricultural areas are unlikely to persist while those near agricultural land can be destroyed by normal agricultural management practices, since canola is a poor competitor.[76].

b. The transferred DNA is stably integrated and intact across all five tested generations of MON 94100 so there is a low likelihood of transgenic escape.[77].

c. The inserted gene, *dmo* codes for the protein dicamba mono-oxygenase, which has been proven through molecular and toxicological analyses as not similar to any known toxin and thus is safe for food and feed consumption.[78].

d. The Project Description Report (PDR) indicates the environmental management plan indicating the possible risk and harm to the environment particularly on biodiversity, as well as the mitigating measures and contingency plan.

DENR-BC's Conclusion

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 canola MON 94100, the DENR-BC considered that the regulated article poses no significant adverse effect to the environment.

DOH-BC's Assessment

a. Oilseed rape was first cultivated in India about 4,000 years ago and has been used to produce low erucic acid rapeseed oil which has been referred to different common names such as canola oil in some countries.[3].

b. Other than the potential to become an opportunist pathogen in immunocompromised hosts, *S. maltophilia* is not known for human pathogenicity. The history of safe exposure of *S. maltophilia* has been repeatedly reviewed during the evaluation of several dicamba tolerant events with no safety or allergenicity issues identified by global regulatory agencies including corn MON 87419, cotton MON 88701, and soybean MON 87708.[1][20][43][35][36][37][38][39][40][41][42].

c. DMO protein levels in various tissues of canola MON 94100 were determined using ELISA. Forage, leaf, grain, and root tissue samples were collected from each replicated plot at all field sites treated with dicamba herbicide. The mean DMO protein level in MON 94100 across all sites was highest in root at 5.0 µg/g dry weight (dw) and lowest in grain at 0.64 µg/g dw .[1][65].

d. Canola MON 94100 contains a demethylase gene from *S. maltophilia* that expresses a dicamba mono-oxygenase (DMO) protein to confer tolerance to dicamba herbicide. DMO protein rapidly demethylates dicamba to the herbicidally inactive metabolite 3,6-dichlorosalicylic acid (DCSA) and formaldehyde. Neither DCSA nor formaldehyde generated by the action of DMO on dicamba pose a significant food or feed safety risk.[1][81][82][83].

e. Compositional data confirmed that grain from MON 94100 is compositionally equivalent to conventional canola, and therefore the food safety of this product is comparable to that of the conventional canola and is unlikely to result in allergic reaction.[1][15][16].

f. Health Canada's opinion deals only with the food use of MON 94100. Issues related to its environmental release and use as animal feed have been addressed separately through existing regulatory processes in the CFIA.[84].

DOH-BC's Conclusion

Based on the evaluation of available literature and dossier documents presented, canola MON 94100 applied for Direct Use as Food, Feed or for Processing (FFP) is as safe as its conventional counterpart except for its herbicide tolerance and hybridization traits. It is also compositionally equivalent to conventional canola with minimal alteration on some nutritional components. Use of this event in its usual context is not expected to pose any new or additional risk to human health.

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

a. Philippines is not producing canola, either GM or non-GM. Thus, it has no contribution to Philippine agricultural production. In terms of consumption and trade, it is very minimal and was declining.[85][86][87][88][89][90][91].

b. The importation of GM canola, specifically canola MON 94100, will not drastically change the current patterns of production, consumption, or utilization of vegetable oil in the country.[85][86].

c. Considering the share of canola oil to the total vegetable oil consumption of the Filipinos, importation of canola MON 94100 will not also affect the current pattern of consumption of vegetable oil. However, granting a permit of canola MON 94100 for direct use as food, feed, or for processing will help the supply of vegetable oil cope up with the growing demand due to increasing population which may result to more stable prices of vegetable oil.[85][56].

d. For trade, since the Philippine is a small country and its importation of canola for use as canola oil is very minimal, allowing the importation of canola MON 94100 will not affect the current pattern of Philippine trade. [85][56].

e. Granting permit of canola MON 94100 for direct use as food, and feed, or for processing will not alter any ethical norms and values in marketing of any ethnic and cultural group in the Philippines.[92].

SEC Expert's Recommendation

After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines, Inc., relevant to canola MON 94100, the SEC expert recommended the approval and issuance of biosafety permit of the said GM product.

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