

ASSESSORS' CONSOLIDATED REPORT ON MONSANTO'S APPLICATION FOR DIRECT USE AS FOOD AND FEED, OR FOR PROCESSING OF COMBINED TRAIT PRODUCT SOYBEAN MON87708 x MON89788

EXECUTIVE SUMMARY

On April 22, 2016, Monsanto Philippines Inc. applied the combined trait product Soybean MON87708 x MON89788 for direct use as a food and feed, or for processing as an original application under the DOST-DA-DENR-DOH-DILG Joint Department Circular No. 1 Series of 2016 (JDC No.1, S2016).

After reviewing the Risk Assessment Report and attachments submitted by the applicant; the Scientific and Technical Review Panel member, Bureau of Animal Industry, and BPI-Plant Products Safety Services Division found scientific evidence that the regulated article applied for direct use as food and feed, or processing has no evidence of interaction on the resulting gene product.

On the matter of gene interaction, the STRP member, BAI and BPI-PPSSD agreed that there is no significant difference between MON87708 x MON89788 and conventional variety. They also agreed that there is no interaction of the protein products DMO [Dicamba (2 methoxy-3, 6-dichlorobenzoic acid) O-demethylase] and CP4 EPSPS (5-Enolpyruvylshikimate-3-phosphate synthase) that can produce new allergens or toxins. It was also reported that both protein products are targeted in the chloroplast of the plant cell.

The assessors also found a complete description of the mode of action of both DMO and CP4 EPSPS. They agreed that these two protein products have distinct mode of action and will not be involved in the same metabolic pathway. Thus, there are no unexpected effects on the metabolism of the plant.

Furthermore, on the subject of gene expression, the assessors agreed that the level of protein expression of both DMO and CP4 EPSPS in the combined trait product MON87708 x MON89788 is almost the same as it was on individually transformed events MON87708 and MON89788.

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 MON87708 x MON89788 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 combined trait product MON87708 x MON89788.

Lastly, 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 VIII, Section 20 of the JDC No.1, S2016, 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, except for the SEC expert, the complete dossier submitted by Monsanto. 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 in relation to their application.

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

STRP ASSESSMENT AND RECOMMENDATION

After a thorough review of the documents submitted by the applicant, the STRP made the following assessment and recommendation:

A. Gene Interaction

The compositional analysis for 42 seeds components of MON 87708 x MON 89788 showed no significant differences between seeds of MON 87708 x MON 89788 and those with the conventional variety (A3525). This clearly showed the lack of interaction in the stacked traits that could have given rise to new allergen or new toxin.

The lack of interaction among gene products was further indicated in the ELISA test which showed lack of differences in the DMO [Dicamba (2 methoxy-3,6-dichlorobenzoic acid) O-demethylase] and CP4 EPSPS (5-Enolpyruvylshikimate-3-phosphate synthase) protein levels between MON 87708 x MON 89788 and its comparators, MON 87708 and MON 89788, respectively.

In addition, even if the gene products DMO and CP4 EPSPS are being targeted in the chloroplast, these enzymes are involved in different pathways. CP4 EPSPS is involved in the shikimic pathway of aromatic amino acid biosynthesis resulting to the reduced binding affinity for glyphosate herbicide whereas DMO is involved in the oxidative demethylation of dicamba, a broadleaf herbicide.

B. Metabolic Pathways

The mode of action of each gene product was completely described in the application submitted by Monsanto. DMO catalyzes the oxidative demethylation of Dicamba, a broad leaf herbicide thereby, conferring tolerance to Dicamba-based herbicides. The DMO protein belongs to the family of Rieske oxygenase proteins. Dicamba oxidation produced the inactive herbicide compounds; 3-6-dichlorosalicylic acid (DCSA) and formaldehyde.

On the other hand, the CP4 EPSPS enzyme confers tolerance to glyphosate herbicide by reducing the binding affinity for glyphosate in the shikimic pathway. The gene encoding CP4 EPSPS was derived from *Agrobacterium sp.* strain CP4. EPSP synthase catalyzes the transfer of enolpyruvyl moiety of phosphoenol pyruvate (PEP) to the 5-hydroxyl of shikimate-3-phosphate (S3P) in the shikimic pathway.

Aside from having different modes of action, the metabolic products are likewise, not involved in the same metabolic pathway. DMO is a Rieske nonheme oxygenase which catalyzes the oxidative demethylation of dicamba to 3,6 dichlorosalicylic acid and formaldehyde. On the other hand, CP4 EPSPS is involved in the shikimic pathway of aromatic amino acid biosynthesis.

Furthermore, the possibility of unexpected effects of the stacked genes on plant metabolism is nil because the data presented by the applicant on compositional analysis of MON 87708 x MON 89788 seeds and ELISA tests showed the lack of interaction in the stacked traits as well as the absence of significant variation in compositional analysis of seeds derived from MON 87708 x MON 89788 and those with the conventional variety (A3525).

C. Gene Expression

Regarding the expression level of the individual proteins, the ELISA test showed that the protein levels of samples derived from seed tissue of MON 87708 x MON 89788 were not significantly different from the protein level found in MON 87708 and MON 89799 which carry the individual proteins, DMO and CP4 EPSPS, respectively. In addition, both proteins are expressed at low levels in the plant, with DMO expressed at an average, 41 ug/g seed dry weight, whereas CP4 EPSPS was expressed at 93 ug/g seed dry weight.

The approved individual events which had already been evaluated showed evidences that the marker genes were not transferred together with the gene of interest into the host genome. Since MON 87708 x MON 89788 were developed through conventional breeding, the transfer and expression of marker genes in the resulting product is unlikely.

The evidences presented by the applicant have shown the absence of interaction between the genes encoding DMO and CP4 EPSPS, such that any effect on the stability and expression level of either gene is not expected.

Based on the scientific evidences presented, there was no indication of any interaction in the resulting products of the regulated article applied for direct use.

BPI-PPSSD ASSESSMENT AND RECOMMENDATION

After a thorough review of the documents submitted by the applicant/proponent, BPI-PPSSD made the following assessment and recommendation:

A. Gene Interaction

There was no significant interaction between MON 87708 and MON 89788 combined through conventional breeding that could produce a resulting product that is allergenic or toxic. Literatures supports the developer's claim regarding the significant difference in the mode of action of DMO and CP4 EPSPS proteins present in MON 87708 x MON 89788. The structures of both proteins presented in the literatures showed no common binding sites and will not lead to the production of new allergen or toxins. Furthermore, the metabolic pathways of DMO and CP4 EPSPS in MON 87708 x MON 89788 are found to be significantly different as presented in the study of Chakraborty et.al. (2005) and Padgette et.al. (1996). EFSA (2015) identified that the presence of the two proteins in combination would not result in interactions that could lead to the production of new protein. The individual newly expressed

proteins or their mixture in the combined trait product has no safety concern with regards to allergenicity. Soybean MON 87708 × MON 89788 is as nutritious as its non-GM comparator and non-GM soybean reference varieties.

In terms of accumulation of gene products, the gene products DMO and CP4 EPSPS will accumulate specifically in the plastids since the *dmo* and *cp4 epsps* genes are designed to encode chloroplast transit peptides which will direct the gene products to the chloroplast. Also, dicamba and glyphosate are structurally different from one another and has no common binding sites between DMO and EPSPS for these substrates.

B. Metabolic Pathways

There was a complete description of the two gene products provided in the application. In addition, the varying mode of action of the two gene products were also described. DMO protein, which belongs to a family of Rieske oxygenase protein, is a part of a three-component system that includes a ferredoxin, a reductase and an oxygenase. With a high specificity, the DMO catalyzes the NADH-dependent oxidative demethylation of dicamba to the non-herbicidal 3,6 dichlorosalicylic acid (DCSA) (D'Orine et.al., 2009; Chakraborty et.al., 2005) while CP4 EPSPS protein, which belongs to the family of EPSPS synthetases, are involved in the biochemical shikimic pathway producing aromatic amino acid in the chloroplasts (Padgett et.al., 1996). It catalyzes the transfer of enolpyruvyl group from phosphoenol pyruvate (PEP) to the 5-hydroxyl of shikimate-3-phosphate (S3P) producing inorganic phosphate and 5 enolpyruvylshikimate-3-phosphate (Alibhai and Stallings, 2001). This mechanism is being inhibited with glyphosate binding which blocks the binding of EPSPS to PEP. CP4 EPSPS, on the other hand, has higher affinity for PEP thus allowing the catalysis to proceed even in the presence of glyphosate (Franz et.al., 1997).

Aside from the difference in the mode of action, the gene products are also not involved in the same metabolic pathway since DMO is involved in the catalysis of demethylation of dicamba into DCSA via three-component enzyme, ferredoxin, reductase and oxygenase while CP4 EPSPS is involved in the shikimate pathway of aromatic amino acids biosynthesis.

Given the difference in the mode of action and the pathway where the proteins are involved, the equivalence in protein levels in the single events (already approved by the BPI) and the combined trait product, there are no unexpected effects of the stacked genes on the metabolism of the plant. Comparison of the levels of DMO and CP4 EPSPS proteins between stacked and single events did not manifest any interaction to trait expression level. Each protein is not designed to alter the soybean plant metabolism (EFSA, 2015). Further, the DMO and CP4 EPSPS proteins are expressed properly in the combined product MON 87708 x MON 89788 as in its relevant single events as shown in Enzyme-Linked Immunosorbent Assay (ELISA). This indicates that the combined gene products are inherited and functioning properly.

C. Gene Expression

On the subject of gene expression, there are no significant differences in the protein expression levels of DMO and CP4 EPSPS in MON87708 x MON89788 and the individually transformation events in seeds of the stacked trait produced in the United States in 2009. History of safe use has been established for the two gene products expressed in single events MON87708 and MON89788 respectively.

In addition, the protein levels of DMO and CP4 EPSPS in MON 87708 x MON 89788 are equivalent to the protein levels expressed in both single events which are already approved by the BPI. DMO was detected at low levels, which constitutes only 0.11% of the total protein present in MON 87708. Hence, the evidence is sufficient to confirm that the DMO and CP4 EPSPS proteins in MON 87708 x MON 89788 in seeds are expressed in low levels.

Aside from the difference in the mode of action, it was also noted that the gene products are not involved in the same metabolic pathway since DMO is involved in the catalysis of demethylation of dicamba into DCSA via three-component enzyme, ferredoxin, reductase and oxygenase while CP4 EPSPS is involved in the shikimate pathway of aromatic amino acids biosynthesis.

Given the difference in the mode of action and the pathway where the proteins are involved, and in addition the equivalence in protein levels in the single events and the combined trait product, there are no unexpected effects of the stacked genes on the metabolism of the plant. Comparison of the levels of DMO and CP4 EPSPS proteins between stacked and single events did not manifest any interaction to trait expression level. Each protein is not designed to alter the soybean plant metabolism (EFSA, 2015). BPI-PPSSD further elaborated that DMO and CP4 EPSPS proteins are expressed properly in the combined product MON 87708 x MON 89788 as in its relevant single events as shown in Enzyme-Linked Immunosorbent Assay (ELISA). This indicates that the combined gene products are inherited and functioning properly.

Based on the scientific evidences presented, there was no indication of any interaction in the resulting gene products of the regulated article applied for direct use.

BAI ASSESSMENT AND RECOMMENDATION

After a thorough review of the documents submitted by the applicant/proponent, BAI made the following assessment and recommendation:

A. Gene Interaction

There was no known interaction between DMO and CP4 EPSPS since they have different modes of action and target/substrates. In addition, they have reported that the two protein products accumulate at the chloroplasts.

B. Metabolic Pathways

The mode of action of both DMO and CP4 EPSPS was sufficiently described in the documents submitted by the applicant/proponent. There were substantial scientific evidences that these two protein products have different mode of action and are not involved in the same metabolic pathway.

It is extremely unlikely that there would be unexpected effects of the stacked genes in the metabolism of the plants given the differences in the mode of action of each gene, different metabolic pathways, similar expressions with the conventional host plant, traits of each gene were inherited and functional in the combined trait products, and other factors considered to conclude as such.

C. Gene Expression

Regarding the expression level of the individual proteins, the mean expression levels of both DMO and CP4EPSPS in single events and stacked event are almost the same.

Both proteins were determined to occur at almost the same range levels in seeds but results do not indicate if they are indeed low since there was no comparison with conventional soybean seed, unless, it is taken that conventional soybean seed has neither DMO nor CP4EPSPS.

The T-DNA II containing the CP4 EPSPS gene cassette, which was used as a selective marker for early event selection was segregated away from the T-DNA I in MON 87708. Therefore, the T-DNA II elements are absent.

There is no expected interaction between the genes or their expressed products. Stability of the inserted genes and expression levels of either one were verified with a validated ELISA on seed tissue of R8 growth stage of MON 87708 X MON89788.

Based on the scientific evidences presented, there was no indication of any interaction on the resulting gene products of the regulated article applied for direct use.

DENR-BC ASSESSMENT AND RECOMMENDATION

After a thorough scientific review and evaluation of the documents provided by the Bureau of Plant Industry (BPI) to the DENR Biosafety Committee within the prescribed period pursuant to the JDC No. 1 S 2016 on the application of Monsanto Philippines Inc. for direct use for feed, food or processing of Genetically Modified Soybean MON87708 X MON89788 tolerant to dicamba and glyphosate herbicides, along with the submitted sworn statement and accountability of the proponent, a biosafety permit may be issued to the proponent provided the conditions set by DENR are complied with.

DOH-BC ASSESSMENT AND RECOMMENDATION

After a thorough scientific review and evaluation of the documents, DOH find sufficient evidence that the regulated article applied for direct use will not pose any significant risk to the health and environment and that any hazards could be managed by the measures set by DOH.

SEC EXPERT ASSESSMENT AND RECOMMENDATIONS

After thorough review of the documents submitted by the applicant/proponent, the SEC Expert made the following assessment and recommendation:

A. Socio-economic Issues

The approval of GM Soybean for Direct Use as Food and Feed or for Processing will be beneficial to meet the demands of the local feeds industry and for other uses. The local soybean production in the Philippines remains minimal and no significant change is expected through MY16/17 (AgroChart, 2016). Hence, the country remains to be an importer of soybean meal (SBM) and the country is the largest market for US SBM. It has been importing soybean meals for the feed industry since 1964 and the

increasing (although fluctuating) imports for the last 50 years shows the importance of soybeans for the feed industry. (<http://www.indexmundi.com/agriculture/?country=ph&commodity=soybean-meal&graph=imports> retrieved on Sept. 14, 2016). SBM imports are forecast to reach 2.5 MMT in MY 16/17 due to the continued consolidation and growing sophistication of the domestic feed-consuming industries.

In addition, forecasts for August 2016/2017 shows that around the world, a total of 122.30 million hectares are planted to soybean which would produce 33.041 million metric tons. It was also noted that the USA is the number one producer of soybeans, being able to produce 110.51 million metric tons (33.45% of the world's production) from 33.60 million hectares of planting area. Interestingly, 87 percent of soybeans from US is genetically modified.

Regarding the concerns on the possible effect on the current production, the importation of GM Soybean will not drastically change the current production of the crop because the current production locally is very minimal and no significant change is expected through MY16/17 (AgroChart 2016). In addition, the importation of GM soybeans as raw materials for the feed industry and other food uses will help meet the local requirements and maintain trade between US and other trade partners.

B. Social Issues

In terms of health concerns, this aspect may not be relevant because the GM Soybean to be imported will not be used for planting, thus its perceived effects on the health of producers and farming communities may not be a valid concern. However, she pointed out that there are a number of literatures which emphasize the negative effects of GM soybeans on the health of consumers.

In addition, it was emphasized that since this regulated article will be used for Direct Use as Food and Feed, or for Processing (FFP), concerns regarding how it may increase structural dependence like access to complementary herbicide, contractual obligation or license cost, the possibility of squeezing out the traditional production and other concerns regarding social cohesion on the GM product are not applicable since the soybean will not be used for planting.

However, the introduction of GM Soybean for FFP will somehow affect the anti-GMO in terms of the food they consume because of the prevalence of GMO foods and GMO-derived foods, thus they are clamoring for labeling of GMO products to guide them in their decision making. There was also a concern raised by the anti-GMO on the negative impact it may bring on the health of consumers and the environment. Granting that the claimed negative effects of GM soybeans are true, then the people's basic need for a safe environment is at stake. Given these perceptions, research must be done to prove or disprove those claims.

C. Ethical Issues

The decision to favor or disfavor the use of GM soybeans or GMO in general is a personal decision. Although there is an international NGO which is very vocal about its stand, this is not the stand of the whole population. Hence, to be fair with those individuals who are against the use of GMO, they have the right to know whether the products available in the market are derived from GMOs, and this can be done through proper labeling of products. Specially so now that the Philippine Supreme Court issued its final ruling on August 18, 2016 which reversed its December 8, 2015 decision that stopped the field testing, propagation, commercialization, and importation of genetically enhanced products in the country

(<http://www.fas.usda.gov/data/philippines-philippine-biotechnology-update> retrieved on Sept. 14, 2016).

However, the STRP refuted the relevance of the concerns on the ideals of human solidarity and equality. Specifically, the importation of GM soybean as raw materials for FFP will not expose the IPs and the weaker groups of society to adverse consequences.

D. Recommendation

Based on the assessment of the above indicators, the SEC expert does not have any socio-economic, ethical, and cultural issues to raise regarding the approval of the applicant's application for biosafety permit for direct use as food and feed, or for processing of Soybean MON87708 x MON89788. The expert recommended for the approval of said application.