

Consolidated Risk Assessment Report of Syngenta Philippines Inc. Corn GA21 Application for Commercial Propagation and for Direct Use as Food and Feed or for Processing

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.

Likewise, in Section 15 of the JDC No.1, S2016, it stated that no regulated article shall be released for commercial propagation unless: (1) a Biosafety Permit for Commercial Propagation has been secured in accordance with this Circular; (2) it can be shown that based on field trial conducted in the Philippines, the regulated article does not pose greater risks to biodiversity, human and animal health than its conventional counterpart; (3) food and feed safety studies show that the regulated article does not pose greater risks to biodiversity, human and animal health than its conventional counterpart, consistent with CODEX Alimentarius Guidelines on the Food Safety Assessment of Foods Derived from the Recombinant-DNA Plants and protocols of the DOH and BAI on feeding trials; and (4) if the regulated article is a pest-protected plant, its transformation event that serves as plant-incorporated protectant (PIP) has been duly registered with the Fertilizer and Pesticide Authority (FPA).

The BPI Biotech Office provided the assessors, except for the SEC expert, 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.

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 RECOMMENDATIONS

Based on the documents submitted by the applicant:

A. Host Organism

Corn contains some amounts of protein, fat, carbohydrates, and dietary fiber. Corn is a very important source of carbohydrate especially for monogastric animals like poultry and swine. In fact, corn grain is usually incorporated in poultry ration at a range of 40-50% to supply the energy needs of these animals. Corn roughage/forage is also well-liked by ruminant animals. They are palatable and feed intake is usually observed to be higher, thus feed conversion efficiency, better.

Corn is also a source of anti-nutrients; however, only few anti-nutrients were reported to occur in corn. Phytic acid reduces the bioavailability of phosphorus, especially in monogastric animals. Phytic acid is a major storage of phosphorus in grains and cereals. Phytic acid can be reduced by cooking and processing. Other anti-nutrients such as raffinose and trypsin inhibitor are not considered nutritionally significant in corn. Raffinose is considered an anti-nutrient due to gas production and associated flatulence which causes discomfort, although it is not toxic. Trypsin inhibitors are present in low levels in corn and not considered nutritionally significant. DIMBOA was also described as a potential toxicant, however, the effects to human and animal after ingestion is still relatively unknown.

Moreover, references suggested that the level of DIMBOA declines rapidly as plant grows, and therefore may not pose serious risks.

About 20% of Filipinos use corn as a staple cereal. Food products are derived from wet milling, dry milling, and distillery as soups, edible oil, flakes, chips, biscuits, sauces, beer, whisky, etc. Sweetcorn is primarily consumed by humans, although the by-products from processing are used as animal feedstuff. Report of the Cluster G09, where Philippines is included, gave an estimated consumption of corn as 16.736 g/kg bw/day for the general population and 32.518 g/kg bw/day for children.

Corn grain, roughage and soilage are also used mainly in animal feed and for processing. Thus, corn enters the food chain in the form of processed products. It is the preferred feed in livestock production as a processed whole grain, as a by-product of the milling industry, or as a silage.

B. The Transgenic Plant

GA21 corn has already food approval in Argentina, Australia/New Zealand, Belarus/Kazakhstan, Brazil, Canada, China, Colombia, European Union, Indonesia, Japan, Republic of Korea, Malaysia, Mexico, Paraguay, Philippines, Russian Federation, Singapore, South Africa, Taiwan, province of China, United States, Uruguay, and Vietnam.

The GA21 corn was produced via microprojectile transformation system and contains the mepsps gene which confers tolerance to glyphosate. Analyses of grain and forage demonstrate that GA21 is nutritionally and compositionally similar and as safe and nutritious as conventional corn. Well-characterized modes of action, physicochemical properties and a history of safe use demonstrate that the mepsps protein in GA21 corn present no risk of harm to humans or livestock.

Consumption pattern is not expected to change with the introduction of GA21 corn in the market. Yes, the amount of corn consumed as food is not likely to change as it is today.

C. Donor Organism

The mepsps sequence have been described. The mepsps gene was derived from a wild type corn (Genbank Accession X63374). Corn is extensively cultivated and has a history of safe use for human food and animal feed. Corn proteins are not known to be significant allergens. Corn has been listed as a less common allergenic food.

All the potentially inserted regulatory sequences including the promoters, intervening sequence, terminator signal, expression cassette, and the pDPG434 transformation plasmid were adequately described. The mEPSPS protein is not known to be toxic nor allergenic.

D. Transformation System

Microprojectile bombardment transformation system was used to produce GA21 corn. Nuclear DNA is the target of genetic modification. The Plasmid Map of Transformation Vector pDPG434 and all the functional elements present on the NotI Restriction Fragment Employed in the Generation of Event GA21 were presented. The plasmid is derived from psK-vector, which is commonly used in molecular biology and is derived from pUC19. A vector map of pDPG434 was presented. The NotI restriction fragment containing the expression cassette was used for the transformation. Their origin is also described. The NotI restriction fragment contains the modified 5-enolpyruvylshikimate-3-phosphate synthase (mepsps) expression cassette but does not contain the origin of replication, the bla gene or the partial lacZ sequence. Carrier DNA was not used.

E. Inserted DNA

The number of transgenic loci of the Event GA21 insert was examined by Southern analysis. This was sufficiently demonstrated using an EcoRV digestion and hybridization utilizing two PCR-generated probes that represent the functional elements contained on the NotI transformation fragment from pDPG434. Results show that the entire GA21 insert is a single locus and is contained on this hybridization band.

The integrity and order of genetic elements within the insertion site was demonstrated as follows: the sequence analysis of the entire GA21 insert showed that the insert is comprised of five contiguous regions derived from the 3.49 kb NotI restriction fragment from pDPG434 used in the generation of GA21 corn. These five contiguous regions are referred to as Copies A through E, in the 5' to 3' direction. Copy A contains the rice actin promoter with a 5' deletion of 695 bp, the actin first exon and intron, the optimized transit peptide, the gene mepsps, and the NOS terminator. Copies B and C are intact versions of the 3.49 kb NotI restriction fragment from pDPG434, except for one base pair substitution in the NOS terminator of copy C. The nucleotide at this location in Copy C is a cytosine (C) instead of the expected guanine (G). Copy D contains a complete rice actin promoter, the actin first exon and intron, the optimized transit peptide, the first 288 bp of mepsps followed by a stop codon, and no NOS terminator. Copy E only contains the rice actin promoter and a truncated actin first exon, with no other elements from pDPG434.

There are 4 DNA sequences (ORFs) that span the junctions between the corn genomic sequence and the GA21 insert that are contained between a start codon (ATG) and a putative stop (TAG, TAA, or TGA) codon. Each of these hypothetical amino acid sequences was evaluated for the presence of alignments and the degree of similarity with allergens and toxins. An assessment of junction sequences using the FARRP database (2015) supports the conclusion that putative amino acid translations show no biologically relevant sequence similarity to any known or putative protein allergens. An assessment of junction sequences using a toxin-specific database created from the global NCBI Protein Database (2015) supports the conclusion that these sequences show no relevant similarity to any known or putative toxins.

The transgene mepsps has only been expressed in GA21 corn which was already approved in the countries listed above. The Southern analysis has sufficiently demonstrated that the genetic elements of the vector backbone are not present in Event GA21 corn. The lack of hybridization shows the absence of any unintended pDPG434 vector backbone sequences being incorporated into GA21 corn during the transformation process.

F. Genetic Stability

Southern analysis was performed to assess the genetic stability of the GA21 corn. Three generations (BC1, BC2 and B3) of Event GA21 corn were isolated and used for Southern analyses. As expected, these three generations showed the same hybridization patterns for the mepsps gene. The results demonstrate that the transgenic locus was normally transmitted over subsequent generations without any aberrations, and thus proves of genetic stability for the transgenic locus of transformation event GA21. The transgenic locus carrying the gene cassette for mepsps gene is stably inherited over subsequent generations of backcrossing.

Seed of three segregating BC generations (BC1, BC2, and BC3) of Event GA21 was sown under standard conditions in a greenhouse. When the plants were eight weeks old they were sprayed with glyphosate herbicide. Plants were scored based on their tolerance to glyphosate application as either glyphosate tolerant (alive) or glyphosate non-tolerant (dead).

Phenotypic data were used to assess the goodness-of fit of the observed phenotypic ratio to the expected phenotypic ratio, using Chi Square (χ^2) analysis with Yates correction factor. This analysis tested the hypothesis that the herbicide tolerance trait segregates in a Mendelian fashion. The critical value of χ^2 to reject the hypothesis at the 5% level is 3.84. Since the Chi squared value is less than 3.84 for all generations tested, the hypothesis that the herbicide tolerance trait behaves in a Mendelian fashion and segregates in a 1:1 ratio is accepted for all generations examined.

G. Expressed Material

The concentrations of mEPSPS proteins in various GA21 corn tissues were quantified by enzyme-linked immunosorbent assay (ELISA) to establish an expression profile for these proteins as produced in GA21 corn. The tissues analyzed were leaves, roots, kernels, pollen and whole plant at four growth stages (whorl, anthesis, seed maturity, and senescence). The tissues were collected from 2 GA21 corn hybrids and their respective near-isogenic non-transgenic controls grown concurrently according to local agronomic practices at four U.S. locations in 2004. Results showed the ranges of mEPSPS protein concentrations observed in each tissue type across all growth stages and locations on a fresh-weight (FW) basis for GA21 corn. The EPSPS concentrations in the negative control samples were either <LOQ (limit of quantification) or <LOD (limit of detection) at the same assay dilutions at which the mEPSPS was quantified in the corresponding transgenic samples.

The GA21 event contains a modified epsps gene from corn. The mEPSPS protein has low affinity for glyphosate, thus when plants expressing the mEPSPS protein are treated with glyphosate, the plants are unaffected. The continued action of the tolerant mEPSPS enzyme provides the plant's need for aromatic amino acids. Glyphosate kills plants by inhibiting the enzyme EPSPS. This enzyme is a critical step in the Shikimic Acid Pathway for the biosynthesis of aromatic amino acids in plants and microorganisms, and its inhibition leads to the lack of growth in plants.

H. Toxicological Assessment

The susceptibility of mEPSPS to proteolytic degradation in simulated mammalian gastric fluid (SGF) containing pepsin was evaluated. No intact mEPSPS (molecular weight ca. 47.5 kDa) in either the corn-derived or microbial sources of mEPSPS was detected following digestion in SGF for 1 minute as assessed by SDS-PAGE and Western blot analysis. After 1 min incubation in SGF, only in the plant derived sample that an immunoreactive lower molecular weight fragment (ca. 6kDa) was detected by Western blot. This protein fragment most likely represents a breakdown product of mEPSPS due to pepsin action and was no longer detectable after 5 min of incubation in SGF. This support the conclusion that mEPSPS expressed in transgenic plants will be readily digested under typical mammalian gastric conditions.

The temperature stability of mEPSPS was also evaluated by incubation of aliquots of an aqueous solution of microbially produced test substance containing the mEPSPS enzyme at 25°C, 37°C, 65°C, and 95°C for 30 minutes and assessing immunoreactivity using ELISA. At 25°C and 37°C, there was little effect on mEPSPS immunoreactivity; ca. 96% and 92%, respectively, of the baseline immunoreactivity remained. At 65°C and 95°C there was a complete loss of mEPSPS immunoreactivity. The data presented in this study support the conclusion that mEPSPS is stable upon heating up to 37°C for 30 min but is unstable upon heating at temperatures 65°C and above, as measured by the loss of immunoreactivity.

Further, the assessment of the mEPSPS amino acid sequence using a comprehensive similarity search of a non-redundant NCBI Protein Database and a Syngenta custom toxin database supports the conclusion that the mEPSPS sequence shows no biologically relevant similarity to any known or putative mammalian protein toxins.

An acute oral toxicity study of mEPSPS in mice was further conducted. There were no effects on clinical condition, bodyweight, food consumption, clinical pathology, organ weight, macroscopic or microscopic pathology that were considered related to the administration of 2000 mg mEPSPS protein/kg bodyweight to male and female mice. In conclusion, the oral administration of 2000 mg mEPSPS protein/ kg bodyweight as a single dose resulted in no treatment related effects.

Finally, the mEPSPS expressed in recombinant *E. coli* was compared by analysis of various functional and biochemical parameters to mEPSPS protein produced in transgenic corn event GA21. Based on these results, it can be concluded that mEPSPS proteins from recombinant *E. coli* and GA21-derived corn are substantially equivalent and that the microbial test substance GA21-0104 is a suitable surrogate for mEPSPS protein produced in GA21.

I. Allergenicity Assessment

To assess evidence of allergenicity, sequence similarity search is done. In the FASTA search, no sequence similarity greater than 35% shared identity over 80 or more amino acids was observed between the mEPSPS amino acid sequence and any entry in the COMPARE database. In addition, results from the exact match search show no alignments of 8 or more contiguous amino acids between the mEPSPS amino acid sequence and sequences in the COMPARE database.

The mEPSPS proteins from both sources (microbially produced and plant produced) were also demonstrated to have the predicted molecular weight of ca. 47.4 kDa. No evidence of any post-translational glycosylation of mEPSPS protein from either source was observed.

In using the maximum protein expression levels in the kernels of the hybrid used in the expression studies, mEPSPS comprises ~0.0092036% of the total weight in kernels. Assuming that the fresh weight of grain is composed of ~9.4% of the total kernel weight (USDA, accessed 2018), then the mEPSPS protein comprises ~0.0092% of the total protein in the kernels. Given the very low levels of expression for mEPSPS in corn, the potential for dietary exposure to mEPSPS via GA21 corn seed is considered minimal.

There is no need to perform the serum screening test. Digestibility study showed that exposure to gastric fluid containing pepsin for 1 minute, completely degraded the test protein. Since there is nothing left for absorption, thus, nothing enters the blood stream.

J. Nutritional Data

The proximates of the GA21 corn plants generally do not statistically differ from the non-transgenic corn plants. All mean levels of corn grain and forage proximate components were within the component ranges published in the literature

The amino acid composition of the GA21 corn plants also do not statistically differ from the non-transgenic corn plants, and that the values are within the ranges presented in literatures.

The levels of the five most abundant fatty acids in grain from the GA21 corn hybrid and the non-transgenic, near-isogenic hybrid were analyzed. A statistically significant difference was observed for 18:2 linoleic acid but no significant differences were observed in levels of the other four fatty acids measured. However, the average levels of all the five measured fatty acids, including 18:2 linoleic acid, were within the ranges reported in the literature.

Lastly, no statistically significant differences between the mineral composition of the forage and of the grain from GA21 corn hybrid and the non-transgenic, near isogenic hybrid were found.

Meanwhile, no statistically significant differences between the antinutrients of the grain from GA21 corn hybrid and the non-transgenic, near isogenic hybrid were also found. The average levels of all the antinutrients in the corn grain were within the ranges reported in the literature.

K. Host Plant Environment

Corn is generally regarded as a highly cross-pollinated crop. The male flowers are borne at the tassel on top of the plant while the female flowers are on the ear shoots around the middle height of the plant. Pollination is generally aided by wind. From the results in multi-location field trials, some pollinators were observed in the trial sites. Pollinators commonly observed in corn fields include syrphid flies, wasps, butterflies and bees. It belongs to Tribe Maydeae, which includes eight genera. It readily crosses with teosinte, the only wild relative of corn which it can cross pollinate. It hybridizes easily with *Tripsacum* under controlled conditions only while *Euchlaena* freely crosses in its native habitat in Central America.

Two accessions of *Zea mays* ssp. *mexicana* were collected in Ilocos Norte and were reported to cross easily with corn. Local study also showed no hybrids were produced when *Zea mays* was crossed with Coix, a close relative of corn present in the Philippines. There are no known sexually compatible cultivated species in the Philippines, However, corn readily produces hybrids with other varieties in the same *Zea mays* species.

For almost 15 years of continuous planting of GT corn, farmers learned to cultivate and plant on slopes/mountain areas that contributed to soil erosion i.e. Quirino Province. The popularity as well as the benefits of the GT corn: Glyphosate on ease of weed management encourage this change of cultivation practices hence, the negative environmental impact. Together with the Department of Agriculture (DA), through the Bureau of Soils and Water Management (BSWM), CropLife, which Syngenta is a member of, developed a project called SCoPSA after convening other agricultural stakeholders. The project aims to enhance productivity level of corn farmers through the promotion of a sustainable land use management that will enhance agricultural livelihood and restore ecological balance in sloping areas of the country cultivated with corn. This project is now a national program that DA and BSWM are implementing in collaboration with the DA Regional Field Offices, DA Agricultural Training Institute, Local Government Units (LGUs), CropLife Philippines, and various non-government organizations (NGOs) in selected areas in the country (CLP, 2017).

Syngenta, though CropLife, provides a continuous and long-term program of trainings to the corn farmers through SCoPSA. Techno-demo farms as training centers were successfully established in selected corn areas such as Nagtipunan, Quirino and Sultan Kudarat, South Cotabato. It is recommended to plant corn only in areas with 1-18% slope to sustain production while addressing erosion issues. Trainings on the safe and sustainable use of crop protection products were also done to maximize product benefit while minimizing any undesirable effect. Training manuals were provided to SCoPSA trainers, extension workers, technicians, and implementors.

Based on the result of the SCoPSA project implementation, farmers and LGUs were found to be highly engaged in establishing more sites and community based techno-demo farms that can benefit various families relying to corn as their main source of livelihood. Results were manifested by numerous requests coming from LGUs seeking assistance to conduct technical briefings and capacity trainings (BSWM, 2016).

In fact, farmers from Nagtipunan, Quirino where the SCoPSA techno-demo farm is being handled by Syngenta, were able to transform deteriorating upland suffering from soil erosion into a flourishing terrain. With the leadership of the Municipal Agricultural and Fisheries Council, the municipality of Nagtipunan, Quirino became the first to institutionalize SCoPSA via SB Resolution No. 272 series of 2017 (CLP, 2019). To date, around 300 farmers are currently practicing what they've learned from SCoPSA trainings in Quirino (H. Marquez, personal communication, August 21, 2019).

L. Consequences of Out-crossing

Teosinte crosses readily with corn and is found in Ilocos Norte. Therefore, the possibility of cross fertilization between cultivated GA21 corn and cultivated teosinte cannot be ruled out in this region. Should cross-fertilization occur between GA21 corn and teosinte then the trait for glyphosate herbicide tolerance may be imparted. This means that teosinte plants derived from the seed product of the cross fertilization may have glyphosate herbicide tolerance. Because teosinte planted in Ilocos Norte is used as animal feed (i.e. silage) the plants are harvested before seed maturity and thus the seeds resulting from the hypothetical cross fertilization would be removed from the environment and would not be propagated. It is possible that the seeds may spill from teosinte before or during harvest, and in this case, result in volunteers. These volunteers are unlikely to persist naturally as the hybrid progeny produce seeds attached to a cob (Ellstrand et al., 2007) and thus are unlikely to naturally release their seeds.

To prevent out-crossing with other corn varieties planted in adjacent fields, time isolation of 25 days is possible based on the biology and reproductive cycle of the corn plant. This was demonstrated in the multilocation field trials.

M. Weediness Potential

Mode of propagation is by seed. But according to Mangelsdorf (1986), corn, as we know it, is a highly domesticated plant. It is the most efficient of all grasses at producing grain, but is unable to survive without human help because it has no way of spreading its seeds. The kernels on an ear of corn cling tightly to the rigid cob, and if the ear was simply allowed to drop to the ground, so many competing seedlings would emerge that in all likelihood, none would grow to maturity.

Corn was not observed to exhibit seed dormancy. Mature seeds easily germinate when moisture is available. During high moisture, corn kernels germinate even when the cob is still attached to the plant. However, with proper storage, seeds will remain viable for a longer period of time.

Days to flowering (50% tasseling and silking) and harvest period were gathered to show time to maturity. Days to flowering was recorded from the two inner rows of each plot. Days to harvest is equivalent to days after planting. Days to flowering showed no significant differences among the entries/families. Flowering slightly differed by location by 1 to 3 days. Corn plants were harvested at 99 to 112 days after planting.

Maturity depends on the corn genotype or variety as different varieties differ in maturity. It is also dependent on the location. Days to flowering (50% tasseling and silking) and harvest period were gathered to show time to maturity. Days to flowering showed no significant differences among the entries/families. Flowering slightly differed by location by 1 to 3 days. Corn plants were harvested at 99 to 112 days after planting.

Corn varieties have been cultivated in the country for over a decade already. To date, there was no record to show that these varieties or the corn plant became weeds in the wild. It has been thoroughly domesticated that it cannot survive without man's aid.

In the multi-location field trials, results show that in general, the agronomic traits such as flowering (tasseling and silking), plant height, and ear height showed no significant differences between GA21 corn versions/families and the isogenic non-GA21 corn hybrid. The multi-location field trials demonstrated that the GA21 technology is a viable option for weed control in commercial corn production. The trait is specific for tolerance against herbicide containing glyphosate. Insect diversity (both pest and beneficial) is not affected by the GA21 trait. Disease occurrence is not impacted by this trait.

N. Secondary and Non-Target Effects

An acute oral toxicity study was conducted for the mEPSPS protein using mouse. The administration of 2000 mg mEPSPS/kg body weight to mice produced no adverse effects.

Meanwhile, insect predators, pollinators, parasitoids, insect pests and scavengers were also studied in the field. The mean number of predators, pollinators, parasitoids, pests, and scavengers collected appeared not to vary between the GA21 and non-GA21 corn plots. No trends can be established. This was observed across locations and seasons. The apparent lack of trend of the insect population collected in the GA21 and non-GA21 corn plots suggested that the Event GA21 corn did not have an impact on insect population. The variation observed can be attributed to high mobility of insect pests.

Insect pests such as corn borer and other lepidopteran pests infested both the GA21 and non-GA21 corn plots in all trial locations. Infestation of earworm, cutworm, semi-looper and armyworm during the early stage of plant growth caused severe feeding and damage to the whorl. Corn plant hoppers were observed as well.

The GA21 field trial shows that the event does not offer genetic advantage against insect pest. The trial has to be protected against insect pests like corn borer and other lepidopteran pests. Moreover, the GA211 corn does not offer protection against corn diseases. The only modified trait expressed by GA21 corn is that of glyphosate herbicide tolerance. GA21 corn offers an effective weed control option since it can withstand glyphosate treatment applied at recommended and at farmers' practice dosage of 160 mL formulated product per 16 Liters of water.

O. Recommendation

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 any significant risk to human and animal health

BAI AND BPI-PPSSD ASSESSMENT AND RECOMMENDATIONS

Based on the documents submitted by the applicant, BAI made the following assessment:

A. Toxicological Assessment

Digestibility study provided indicated that mEPSPS is degraded in simulated gastric fluid (SGF) within 5 minutes of incubation. The susceptibility of mEPSPS protein to proteolytic degradation was evaluated in the simulated mammalian gastric fluid (SGF) containing pepsin using SDS-PAGE and Western Blot Analysis (Graser, 2005). Heat stability studies indicate that based on the bioassay data provided Cry1F protein was deactivated after exposure to 65 °C and above for 30 min (Mims, 2007).

Bioinformatics analyses using BLASTP sequence alignment program and NCBI toxin database provided by the developer indicated that mEPSPS has no significant homology to any known toxin (Bauman, 2018).

Further, acute oral toxicity study provided by the developer indicated no treatment related adverse effects on survival, clinical observations, body weight gain, food consumption or gross pathology of mice administered with mEPSPS protein. The NOAEL for mEPSPS is 2000 mg/kg body weight.

Lastly, the mEPSPS protein was produced in recombinant *E. coli* and compared by analysis of various functional and biochemical parameters to mEPSPS protein produced in transgenic corn event GA21. SDS-PAGE and western blot analysis have demonstrated that the microbially-derived and the GA21 maize-expressed mEPSPS proteins are equivalent regarding their molecular weight and their immunorecognition (Graser, 2005).

B. Allergenicity Assessment

The results of bioinformatics analysis provided by the developer using FASTA sequence alignment tool showed that mEPSPS protein has no homology to any known allergens in the COMPARE database. Likewise, no alignments of 8 or more contiguous amino acid was reported (Bauman, 2018; Graser, 2005). The plant-produced and microbially-produced mEPSPS protein have the predicted molecular weight of ca. 47.4 kDa, have the same N-terminal sequence and showed a specific activity of ca 734 μ /mg and 1560 μ /mg, respectively.

The mEPSPS protein showed no evidence of any post-translational glycosylation and the predicted molecular weight of mEPSPS is 47.4 kDa.

Lastly, based on the concentration of mEPSPS protein in kernels of the hybrid and % fresh weight of total protein in GA21, the percent of mEPSPS protein in one gram of GA21 kernels is 0.0092% which represents a very small portion of total protein in GA21 harvested kernel (Hill, 2006). Hence, the margin exposure of humans or animals to risk of consuming high dosage of mEPSPS is high.

C. Nutritional Data

Compositional analysis indicated no significant differences in the proximate and fiber levels in forage and grains of GA21 corn and the non-transgenic near isogenic corn except for the carbohydrates levels in forage (Kramer and Launis, 2006). There were also no significant differences in the levels of minerals, amino acids, fatty acids and vitamins of GA21 grains and the non-transgenic near isogenic corn except for linoleic acid, vitamin A and vitamin B9 (Kramer and Launis, 2006). The mineral levels of GA21 corn is not significantly different from the mineral levels of the non-transgenic near isogenic corn. No significant differences were also found between all anti-nutrient and secondary metabolite levels of GA21 and the non-transgenic near isogenic corn. Furfural and raffinose levels were below limit of quantitation (LOQ). Trypsin inhibitor data were not suitable for statistical analysis since three (3) samples were below LOQ (Kramer and Launis, 2006).

Soaking, cooking, enzyme or solvent treatment and irradiation can remove raffinose from corn food and feed. Secondary plant metabolites such as furfural can be denatured by heat. Ferulic acid and p-coumaric acid are also found in vegetables and has a history of safe use as it is being used as flavoring in foods, as supplements and in traditional Chinese herbal medicine (OECD, 2002, Section III and IV, pp. 28-30). Trypsin inhibitors are proteinaceous in nature and can be denatured by heat (OECD, 2016, Section III. p. 32)

The developer did not conduct nutritional comparison of GA21 corn with range of commercial varieties, however all mean values were within the literature ranges (Kramer and Launis, 2006).

Statistical differences observed between GA21 and non-transgenic corn were not biologically relevant since all proximate levels, nutritional levels and anti-nutritional levels of GA21 were still within the range of literature values (Kramer and Launis, 2006).

D. Recommendation

Find 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 human and animal health

DENR ASSESSMENT AND RECOMMENDATION

After a comprehensive review and evaluation of the documents, including the scientific evidence from references and literature submitted by Syngenta Philippines, Inc. on its renewal application for Commercial Propagation and Direct Use of Corn (GA21), hereunder are the observations and appropriate actions:

1. The regulated article is considered substantially equivalent to its conventional counterpart for its history of safe use as food in twenty-three [Argentina, Australia, Brazil, Canada, China, Colombia, European Union, Indonesia, Japan, Malaysia, Mexico, New Zealand, Paraguay, Philippines, Russia, Singapore, South Africa, South Korea, Taiwan, Thailand, United States, Uruguay, and Vietnam] (23) countries and as feed in seventeen [Argentina, Brazil, Canada, China, Colombia, European Union, Japan, Malaysia, Paraguay, Philippines, Russia, South Africa, South Korea, Turkey, United States, Uruguay, and Vietnam] (17) countries. It has also been previously approved for commercial propagation in ten [Argentina, Brazil, Canada, Japan, Paraguay, Philippines, South Africa, United States, Uruguay, and Vietnam] (10) countries (International Service for the Acquisition of Agri-Biotech Applications GM Approval Database, 2019);
2. The genetic stability of the transgenic crop was tested over multiple generations wherein the hybrids of the regulated article crossed and backcrossed with inbred were tested for glyphosate herbicide tolerance. Furthermore, through southern blot analysis, the progenies across four generations were analyzed to verify the stability of the inserted genes, in which the genes show identical banding patterns (Canadian Food Inspection Agency, 1998);
3. The glyphosate herbicide tolerance traits of the regulated article do not alter nor enhance the persistence, invasiveness, or weediness of the crop relative to its conventional counterpart (Biosafety Clearing-House, 2002).
4. The direct use of the regulated article whether for food, feed or for processing will not cause any significant diverse effect on the environment and biodiversity. The transgenic crop will not increase its weediness potential in case the seeds spill out into the environment because the mEPSPS proteins produced by the transgenic crop will degrade upon exposure to the natural environment and general condition that is high temperature, 65 oC and above, varying pH, enzyme digestion, etc. (Mims, 2007)
5. The amino acid sequence of the mEPSPS protein has no similarity with known toxin sequences based on bioinformatics assessment through Basic Local Alignment Search Tool (BLAST) and Fast Allignment (FASTA) algorithm (EFSA, 2015).
6. The project description report (PDR) discusses the specified environmental management plan indicating the possible risk and harm to the environment and biodiversity as well as the mitigating measures and contingency plan. Furthermore, 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 port, roads, railways, etc.) is not conducive for plant growth. Also, corn is a highly domesticated plant that requires

human intervention for it to persist in the environment (OECD, 2013 and Raybould, et al, 2012)

Based on the evaluation and review of literature cited, the DENR-BC considered the regulated article safe to the environment, particularly on non-target organisms and hereby submits the technical report relative to the renewal application of Syngenta Philippines, Inc. for Biosafety Permit for commercial propagation and direct use of Corn GA21.

DOH ASSESSMENT AND RECOMMENDATION

After a thorough review and evaluation of the documents provided by the proponent, Syngenta Philippines, Inc., through the Bureau of Plant Industry (BPI), in support of their application for approval for Commercial Propagation (CP) and Direct Use as food and feed, or for processing (FFP) of Corn GA21. I/We,

Find that the regulated article applied for Commercial Propagation (CP) and Direct Use as food and 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.

1. Find that the regulated article applied for Commercial Propagation does not changes in the usual practices as described in the phases/stages of biotechnology activities. As such the regulated article is as safe as its conventional counterpart and is not expected to pose any significant risk to human and animal health and environment.
2. Scientific pieces of evidences from Toxicity studies and references, find that the regulated article will not cause significant adverse health effects to human and animal health.
3. Dietary exposure to the regulated article is unlikely to result allergic reaction.
4. The regulated article is not materially different in nutritional composition from that of non-transgenic com or the conventional corn.
5. Scientific pieces of evidences from provided references i.e. literature show that regulated article applied for Commercial Propagation is as safe as its conventional counterpart and shall not pose any significant risk to human and animal health and on the environment.
6. It is suggested that the Bureau of Plant and Industry (BPI) ensure the following :
 - a) Strict monitoring of the regulated article from port of entry to the trader's/importer's storage/warehouse as stated in Section 32 of the Joint Department Circular Number 1, series of 2016.
 - b) The BPI to include in the issuance permit for the release of this product the following conditions :
 - i. Any spillage (during unloading and loading/hauling and transport, unloading and storage) shall be collected and cleaned up immediately.
 - ii. Transportation of the consignment from the port of entry to any destination within the country shall be in closed containers.
 - iii. There shall be a clear labeling of the product from importation down to all levels of marketing stating that it is for the purpose of commercial propagation

Based on the above considerations and with the submitted sworn statement and accountability of the proponent, this recommendation is being submitted to BPI related to the processing and issuance of a Biosafety Permit for Commercial Propagation (CP) and Direct Use as food and feed, or for processing (FFP) of Corn GA21.

SEC ASSESSMENT AND RECOMMENDATIONS

Based on the two SEC expert review of the SEC questionnaire answered by the applicant:

GA21 is a genetically modified corn which expresses glyphosate tolerance. The trait was introduced using the microprojectile bombardment transformation with wild corn as the source of the mepsps gene.

In the Philippines, corn is a major crop used for food and feeds by about 20% of the Filipinos. It is the second most important food crop (after rice), and the major source of income for one-third of farmers numbering about 1.8 million. It is also the primary source of feed for the country's poultry and livestock industry. It is also being increasingly used in the manufacturing sector. Corn production dipped in 2015 and 2017 but increased in 2018. (<https://www.indexmundi.com/agriculture/country=ph&commodity=corn&graph=production>)

Meanwhile, for the period 2013-2017, consumption decreased in 2015 but picked up in 2016 and 2017. (<https://www.indexmundi.com/agriculture/country=ph&commodity=corn&graph=domestic-consumption>). The 2013-2017 data show that production has always been less than consumption. This implies the need to increase corn production or import corn and corn products to meet the demand for consumption.

GA21 will not drastically change the current patterns of production, consumption/utilization of corn. The Philippines' importation of corn in 2014 to 2018 fluctuated. In 2014, corn importation decreased by almost -15% but increased again in 2015 with a growth rate of 19%. Importation continuously decreased in 2016 and 2017 by -18% and -34%, respectively.

GM corn exhibits increases in yield; there was a 34-37% yield advantage over the conventional corn and a 19% average (range of 14-21%) increase in yield over the past 2 seasons (wet season 2003 and dry season 2003-2004). Similarly, there was a 19% yield advantage of GM corn over the conventional hybrid corn from 2003 to 2011 (Yorobe and Quicoy, 2006). The yield advantage seemed to favor farmers with average to high yields, and produce positive yield difference across seasons (Gonzales et al., 2009).

Farm management will be the same except for the over the top glyphosate herbicide application in corn. This is possible since GA21 corn tolerates glyphosate herbicide application.

Lastly, the adoption of GM corn has mainly resulted in lower cost of production, although yield gains from improved weed control has been noticeable. Data from 1996-2012 shows that in the Philippines, the average cost of technology falls around \$24-47 (Php1,320 – Php2,585) per hectare. The average farm income benefit (after deduction of cost of technology) is \$40 (Php2,200) per hectare (Brookes and Barfoot, 2014).

Recommendation

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