ASSESSORS' CONSOLIDATED REPORT ON MONSANTO PHILIPPINES INC.' SUGARBEET H7-1 APPLICATION FOR DIRECT USE AS FOOD AND FEED, OR FOR PROCESSING

EXECUTIVE SUMMARY

On August 23, 2019, Monsanto Philippines Inc. submitted sugar beet H7-1 for direct use, as original application under the DOST-DA-DENR-DOH-DILG Joint Department Circular (JDC) No. 1 Series of 2016.

After reviewing the Risk Assessment Report and attachments submitted by the applicant, the Scientific and Technical Review Panel (STRP), Bureau of Animal Industry, and BPI Plant Products Safety Services Division concurred that sugar beet H7-1 is as safe as its conventional counterpart.

The Department of Health – Biosafety Committee (DOH-BC), after a thorough scientific review and evaluation of documents related to Environmental Health Impact, concluded that sugar beet H7-1 is safe as its conventional counterpart and shall not pose any significant risk to human health.

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 UPLB. The SEC expert, on the other hand, was provided with special questionnaire on socio-economic, ethical and cultural considerations that have been addressed by UPLB in relation to their application.

INFORMATION ON THE APPLIED EVENTS

The purpose of this sugar beet event H7-1 biosafety permit application is for Direct Use as Food, Feed or Processing (FFP).

Roundup Ready® sugar beet event H7-1 produces 5-enolpyruvylshikimate-3-phosphate synthase protein from *Agrobacterium* sp. strain CP4 (CP4 EPSPS) that confers tolerance to glyphosate, the active ingredient in the Roundup® family of agricultural herbicides. Use of the Roundup Ready® sugar beet system -- planting Roundup Ready® sugar beet event H7-1 and subsequent application(s) of a Roundup® agricultural herbicide -- can simplify and improve weed management practices in sugar beet production.

Sugar beet event H7-1, which was developed through *Agrobacterium*-mediated transformation, has been approved in the Philippines for direct use as food and feed, or for processing since 2005 by the DA – BPI.

Approval of the permit for direct use for food, feed and for processing of sugar beet event H7-1 will enable the entry of this product into the Philippines for food, feed, and processing purposes.

Countries Where Approvals Have Been Granted

Country	Food	Feed	Cultivation
	direct use or processing	**direct use or processing**	**domestic or non-domestic use**
Australia	2005		
Canada	2005	2005	2005
China	2009	2009	
Colombia	2005	2010	
European Union	2007	2007	
Japan	2003	2005	2007
Mexico	2006		

® Roundup and Roundup Ready are registered trademarks of Monsanto Technology LLC.

New Zealand	2005		
Philippines	2005	2005	
Russia	2006	2011	
Singapore	2014	2014	
South Korea	2006		
Taiwan	2015		
United States	2004	2004	2005

Source: isaaa.org/gmapprovaldatabase/event/default.asp?EventID=224

STRP's Assessment

1. **Host Organism**

   a. Sugar beet is an important crop in the US. It is processed into refined sugar for human consumption while molasses and pulp are used for animal feed [1][2].

   b. There has not been found any anti nutritional or other adverse effect to human or animal health during its long history of safe use [2][3].

2. **Donor Organism**

   a. The donor organism is *Agrobacterium* sp. strain CP4, which is a common soil bacterium and is not commonly allergenic [4][5][6][7].

   b. The *cp4 epsps* gene derived from *Agrobacterium* sp. has been well described and used as a natural source of tolerance to glyphosate [5][6][7][8].

3. **Transformation System**

   a. The plasmid vector PV-BVGT08 was used in the transformation of sugar beet H7-1 which contains the cp4 epsps gene coding sequence regulated by a 35S promoter (P-FMV) [4][9][10].

b. The CP4 EPSPS protein is not known to be toxic or allergenic, and is functionally equivalent to native plant EPSPS except for lack of affinity for glyphosate [11][12].

c. The *Agrobacterium*-mediated transformation was used to generate the sugar beet H7-1, and the target of modification was the genomic DNA. A single copy of the T-DNA sequence was integrated into the genome at a single locus [13][14][15].

d. Bioinformatics analyses of the putative polypeptides or proteins possibly produced from the open reading frames (ORFs) showed that the sequences are unlikely to produce allergenic or toxic properties or other adverse biological effects [16].

4. Food and Feed Safety

a. The susceptibility of the CP4 EPSPS protein was assessed using Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF). The SDS-PAGE and western blot analyses indicated that the protein is rapidly digested in SGF within 15 seconds [17][18].

b. Heat inactivation studies were performed and the estimated T50 result for functional activity of CP4 EPSPS is below 15 minutes [19].

c. Bioinformatics analyses showed that CP4 EPSPS does not have any similarity to known proteins that exhibit toxicity or pose potential health hazards [5][20].

d. Acute oral gavage of CP4 EPSPS was performed, and results indicated that the protein does not have similarity to known toxin or any anti-nutritional factor. The reported No Adverse Effect Level (NOAEL) was 572 mg/kg [5][21][22].

e. The bioinformatics assessment of the CP4 EPSPS protein demonstrated the absence of sequence similarity to proteins known to pose human health risks [19][23][24].

f. The inserted protein comprises only 1.44% of the total protein content of sugar beet [25][26][27].

g. There were no observed statistically significant differences in the proximate analyses performed between the sugar beet H7-1 and the non-transgenic and commercial varieties except for the mean level of dry matter in top tissue [28][29].

h. No difference was observed in the nutrient quality analyses of the sugar beet H7-1. The key nutrients and other components are compositionally equivalent to the non-transgenic control [28][29].

STRP's Conclusions

After a thorough review of the new studies submitted by Bayer CropScience, Inc., for sugar beet H7-1 application for direct use as food and feed or for processing, the STRPs found that the new studies submitted by the applicant will not affect the safety of sugar beet H7-1.

The applicant is hereby requested to provide necessary data on the safety of sugar beet H7-1 for direct food, feed, or processing use in the Philippines when requested by the concerned regulatory agency [30].

Furthermore, this post-approval surveillance of new scientific findings of peer-reviewed literature or article publications is a good practice that we may scout potential reports that may have bearing on previously reached food/feed or environmental safety conclusions of the approved product. As we know, science for example biotechnology, is a very dynamic field.

With regard to the submitted review paper, the paper reviewed the suitability of sugar beet crop to glyphosate-resistant technology and mentioned some points namely:

(1) none of the herbicides registered for use in this crop was very effective without risking crop injury;
(2) sugar beet cannot be grown in the same field year after year owing to disease concerns and thus requires a 3–4-year rotation;
(3) pollen-mediated gene flow is negligible from the sugar beet crop because it is a biennial and harvested before it flowers;
(4) the processing of harvested roots to extract the sucrose rapidly degrades the DNA in the extracted raw juice and subsequent refining so that no DNA is present in the finished sugar;
(5) studies have shown that processed GR sugar beet is identical to non-GR sugar beet, as well as cane sugar.

Although there are challenges with pollen-mediated gene flow in sugar beet seed production areas (primarily in western Oregon in the US) because of the presence of other crops producing *Beta vulgaris* seeds, still, GR sugar beet has provided a tremendous improvement in the ability to control weeds in sugar beet. But like what the review paper said, as a word of caution, every distributor and farm that uses glyphosate in the sugar beet production must implement herbicide resistance management practices, or else, the future of GR sugar beet may be put in peril [30].

Moreover, according to the review made by Morishita (2016), studies have shown that the use of GR sugar beet has gained acceptance by growers throughout the United States. Compared with GR corn, soybean, cotton and alfalfa, the adoption rate was much faster with GR sugar beet nationwide. Sugar beet is arguably the best crop in terms of genetic modification for resistance to glyphosate for the following agronomic reasons:

1. As a minor crop, there were limited herbicides registered for use, and none of these was very effective without increasing the risk of crop injury.

2. Sugar beet cannot be grown in monoculture, unlike corn and soybean, because soil-borne diseases essentially prevent it. Thus, most sugar beet is grown in a three or more-year crop rotation.
3. Sugar beet is a biennial plant, so pollen-mediated gene flow is not an issue because the crop is harvested after the first season of growth.
4. Processing harvested roots to extract sucrose degrades DNA in the raw juice and subsequent refining so that no DNA is present in the finished sugar product.
5. Processed GR sugar beet is identical to non-GR sugar beet, as well as cane sugar. [30]

Klein et al. (1998) also reported that during the manufacturing process of sugar, each step of the process proved to be very efficient in the removal of nucleic acid and therefore, sugar obtained from conventional and transgenic sugar beet is indistinguishable or substantially equivalent with respect to purity [31].

In addition, Kniss (2010) reported that sugar content was similar between the two sugar beet systems. Sugar beet root yield showed that there is a 17% increase compared with conventional sugar beet [32].

After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines, Inc. relevant to sugar beet H7-1, the STRPs 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 and the environment.

BAI's Assessment

1. **Toxicological Assessment**

   a. The digestibility study of CP4 EPSPS using SDS-PAGE and western blot analysis showed that more than 95% protein was digested in SGF within 15 seconds [18][33].

   b. The estimated T_{50} result of CP4 EPSPS is less than 15 minutes, based on the functional activity assay and SDS-PAGE result [19].

   c. The bioinformatics analysis of the CP4 EPSPS using sequence alignment tool indicated that the protein is not significantly like any known toxins [35][37][38].

   d. Acute oral gavage was performed, and the no observable adverse effect level (NOAEL) was 572 mg/kg [5][21][22].

2. **Allergenicity Assessment**

a. The results of the bioinformatics analysis showed that the CP4 EPSPS protein lacks sequence similarity with known allergens or allergenic proteins in the ALLERGEN3 database [9][23].

b. The CP4 EPSPS protein represents about 1.44% of the total protein of sugar beet H7-1 roots on a dry weight basis [25][26][27].

2. Nutritional Data

a. For the proximate analysis of sugar beet H7-1, significant differences were observed in the mean level of dry matter in the top tissue, but these are not considered biologically relevant and are within the 99% tolerance interval [28][29][39].

b. Compositional analysis was performed, and results showed that there were no differences found in the vitamins and mineral composition of the transgenic and non-transgenic sugar beet [28][29].

c. The results of the comparison study between sugar beet H7-1 and commercial varieties indicated that there is a significant difference in mean value obtained in polarization, but the data is within the literature range [28][29].

BAI's Conclusions

After a thorough scientific review of technical documents regarding new studies conducted on sugar beet H7-1 and submitted by Monsanto Philippines Inc. applied for direct use as food and feed, or for processing, the BAI agrees with the applicant's claim that the gene modification will not affect the safety of sugar beet H7-1 as supported by the new studies submitted by the applicant [30].

The BAI asked if the GR sugar beet mentioned in the new study provided is similar to the sugar beet H7-1 because according to ISAAA, there are three (3) kinds/applications of GR sugar beets [30]. Monsanto responded that the only biotech GR sugar beet product that has been commercialized in the U.S. and Canada is sugar beet H7-1. Therefore, the study cited in the ISAAA publication is referring to sugar beet H7-1.

Also, BAI stated that the attached study showed that the use of glyphosate resistant sugar beet has performed its intended purpose of controlling weeds, however, it mentioned GR sugar beet in general and is not specific to sugar beet H7-1. If the developer could provide more related studies specific to H7-1, that would be better [30].

In response, Monsanto clarified that the "No Adverse Effect" assessment for H7-1 sugar beet was conducted using publications from journals that are included in the Web of Science℠ database, accessible through the Web of Knowledge℠ platform, a product of Thomson Reuters. The web-based interface allows for a customized search using

keywords in a certain combination. The key words used for this search already included "H7-1".

Moreover, BAI said that the agronomic reasons clearly explain why it is the best crop in terms of genetic modification for resistance to glyphosate. Changes in weed management strategies should be considered by the technology adopter as well the developer. In the Philippines however, it is only applied for direct use as such this may be a little concern, but constant post approval monitoring should always be performed in compliance with relevant guidelines [30].

Monsanto further explained that the commodity products from sugar beet H7-1 produced in the U.S. for domestic use and export to countries such as the Philippines only include highly refined sugar, molasses, and dried pulp. Therefore, post approval monitoring of sugar beet H7-1 in the Philippines will be monitoring non-viable materials, which will be the responsibilities of the sugar beet importers.

Lastly, the BAI stated that, in the letter submitted to BPI, the developer mentioned "When issues have surfaced in scientific literature concerning the safety of sugar beet H7-1, other information has emerged that reaffirmed the earlier conclusion of negligible risk". For clarity and assurance on this matter, the developer should provide at least a matrix showing what are these issues that have surfaced and the corresponding literature reaffirming its negligible risk [30].

The applicant, Monsanto Philippines Inc., further signified that summarizing this "No Adverse Effect" assessment for sugar beet H7-1, there is no evidence from this body of independent, peer-reviewed literature on sugar beet H7-1, which raises any safety issues. After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines, Inc. relevant to sugar beet H7-1, the BAI found scientific evidence that the regulated article applied for animal feed is as safe as its conventional counterpart and shall not pose any significant risk to animal health.

BPI PPSSD's Assessment

1. **Toxicological Assessment**

    a. The SDS-PAGE and western blot analysis confirmed that >95% of the CP4 EPSPS protein was digested in SGF within 15 seconds [18].

    b. The CP4 EPSPS protein was rapidly degraded in SGF and is unlikely to pose a human health concern [18].

    c. Functional activity assay and SDS-PAGE demonstrated the effect of heat treatment on the activity of CP4 EPSPS protein. The T50 result is below 15 minutes [19].

    d. The amino acid sequence comparison with non-redundant protein sequences database using BLASTp showed no significant homology of CP4 EPSPS to any known toxin [35][36].

e. The acute oral toxicity study of CP4 EPSPS in mice showed no treatment-related effects on survival, clinical observations, body weight gain, food consumption or gross pathology. The No Observable Adverse Effect Level (NOAEL) is 572 mg/kg [22].

2. Allergenicity Assessment

a. The bioinformatics analysis of the CP4 EPSPS protein did not yield any significant homology to any know allergen above 35% shared identity in the database [35][40].
b. The level of CP4 EPSPS in sugar beet H7-1 and the amount of total protein indicates that CP4 EPSPS comprises 1.44% of the total protein [25][26][27].

3. Nutritional Data

a. Compositional analysis indicates that there were no statistical differences between the proximate analysis of sugar beet H7-1 and non-transgenic sugar beet that can be considered biologically relevant. All values were within the range of commercial varieties and literature values [28].

b. The results of comparison studies between the sugar beet H7-1 and commercial varieties indicated that all mean values were within the range of eight commercial varieties grown in the same environmental condition [28].

4. **Post-surveillance report**

In spite of the proponent's inability to provide the requested information by the DA - Biotech Committee (DA-BC) on the existing post-surveillance of the regulated articles in other countries that has approved its use as food, they presented in writing a rationale on why the countries such as Australia and New Zealand do not conduct post-market surveillance for food safety. FSANZ does not consider post-market surveillance for food safety as a practical and effective risk management option since the pre-market assessment should already address the issue on the safety of the GM product. In our case, MON 15985 x MON 1445, MON 88913 and H7-1 were already subjected to food safety risk assessment wherein based on the weight of evidence, the regulated articles are as safe as, and is substantially equivalent to its conventional counterparts.

Should the rationale for the post-market surveillance be that the GM product may pose long term adverse effects on human health, chronic health problems are influenced by a multitude of factors that are not specifically or solely associated with consumption of food. If this is the case, the relevance and impact of the data

that will be attained should be proportional to the cost of establishment of analytical methods and infrastructures for the post-market surveillance.

Such justification is adherent to the multi-factor decision making approach indicated in FAO Guidance Materials for risk management wherein scientific information on health risks and other factors including economical factors are needed to be considered and weighed in selecting the preferred risk management actions such as the post-surveillance monitoring.

BPI PPSSD's Conclusion

After a thorough review of the new studies submitted by Monsanto Philippines, Inc. for sugar beet H7-1 application for direct use as food and feed and for processing, the BPI-PPSSD found that the new studies submitted by the applicant will not affect the safety of sugar beet H7-1.

The study referred by the applicant discussed how glyphosate-resistant (GR) sugar beet and conventional sugar beet differs relative to their weed management control and yield. Conventional sugar beet depends highly on heavy application of herbicides to control weed growth which leads to crop injury. The introduction of glyphosate-resistant (GR) sugar beet "showed distinct advantages for controlling weeds in [conventional] sugar beet without injury to the crop". The author further mentioned that the processing of GR sugar beet into refined sugar degrades DNA in the process making it identical to both conventional sugar beet and cane sugar. However, the sustainability of GR sugar beet farming is threatened by the consequent existence of GR weeds. Hence, the study submitted by the applicant will not affect the conclusion stated in the risk assessment report (RAR) for sugar beet H7-1 [30].

Upon review of the provided materials of Monsanto Philippines, Inc. and other literature, weight of evidence approach indicates that sugar beet H7-1 is as safe as its conventional counterpart with regards to substantial equivalence and food safety.

DOH-BC's Assessment

After a thorough review and evaluation of the documents provided by the proponent, Monsanto Philippines Inc., through the Bureau of Plant Industry (BPI) in support of their application for approval for direct use as food and feed, or for processing (FFP) of sugar beet H7-1, the DOH-BC finds that the regulated article applied for direct use as food, feed or for processing is as safe as its conventional counterpart and shall not pose any significant risk to human health.

The following are the observations and recommendations:

1. Scientific pieces of evidence from toxicity studies and references, find that the regulated article will not cause significant adverse health effects to human health;

2. Dietary exposure to the regulated article is unlikely to result in allergic reactions;
3. The regulated article is as safe as food or feed derived from conventional sugar beet varieties;

The regulated article is not materially different in nutritional composition from that of the non-transgenic sugar beet or the conventional sugar beet.

DOH-BC's Conclusion

After a thorough review of the new studies submitted by Bayer CropScience, Inc. for sugar beet H7-1 application for direct use as food, feed or for processing, the DOH-BC found that the new studies submitted by the applicant will not affect the safety of sugar beet H7-1 [30].

SEC Expert's Assessment

a. The applicant was able to provide sufficient information to show that sugar beet has been one of major sources of refined sugar in the market. The country has been constantly supplementing its demand for refined sugar with imports. Approval and issuance of biosafety permit for sugar beet event H7-1 would be an opportunity to boost production of processed sugar for local consumption.

b. The applicant was able to justify that the GM product would not drastically affect the current patterns of production, consumption/utilization (as food, feed, fiber, fuel), and trade since importation of the GM commodity will only be for the purpose of processing so as to meet the country's growing demand for centrifugal sugar. An increase in the eventual supply of processed sugar will result in price adjustments that can favor consumers of sugar-based products.

c. The applicant's expression of not intending sugar beet H7-1 to be commercially grown and marketed for propagation and cultivation addresses concerns about any effect on cultural practices of a specific ethnic and cultural group.

SEC Expert's Recommendation

After a thorough and scientific review and evaluation of the documents provided by Monsanto Philippines, Inc., relevant to sugar beet H7-1, the SEC expert recommends for the approval and issuance of biosafety permit of the said GM crop.

REFERENCES

[1] Monsanto and KWS Petition to U.S. FDA. 2003. Safety, Compositional and Nutritional Assessment of Roundup Ready® Sugar beet Event H7-1. Monsanto Document #03-SB-094F. Monsanto Company, St. Louis, Missouri and KWS SAAT AG, Einbeck, Germany. Part VII Section 2 (Pages 65-66).

[2] OECD. 2002. Consensus document on compositional considerations for new varieties of Sugar beet: Key food and feed nutrients and antinutrients. ENV/JM/MONO (2002)4. Organisation for Economic Co-operation and Development, Paris, France.

[3] Monsanto and KWS Petition to U.S. FDA. 2003. Safety, Compositional and Nutritional Assessment of Roundup Ready® Sugar beet Event H7-1. Monsanto Document #03-SB-094F. Monsanto Company, St. Louis, Missouri and KWS SAAT AG, Einbeck, Germany. Part VII Section 3.2 (Page 74).

[4] Monsanto and KWS SAAT Ag. 2003. Safety Compositional and Nutritional Assessment of Roundup Ready Sugar beet Event H7-1. Monsanto #03-SB-094F Monsanto Company 709 Chesterfield Parkway North, St Louis, MO 6317.

[5] Harrison, L.A., M.R. Bailey, M.W. Naylor, J.E. Ream B.G. Hammond, D.L. Nida, B.L. Burnette, T.E. Nickson, A. Mitsky, M.L. Taylor, R.L. Fuchs and S.R. Padgette. 1996. The expressed protein in glyphosate-tolerant soybean, 5-enolypyruvylshikimate-3-phosphate synthase from Agrobacterium sp. strain CP4, is rapidly digested in vitro and is not toxic to acutely gavaged mice.

[6] Klein, J., J. Altenbuchner and R. Mattes. 1998. Nucleic acid and protein elimination during the sugar manufacturing process of conventional and transgenic Sugar beets. Journal of Biotechnology 60:145-153.

[7] Padgette. 1996. The expressed protein in glyphosate-tolerant soybean, 5-enolypyruvylshikimate-3-phosphate synthase from *Agrobacterium* sp. strain CP4, is rapidly digested in vitro and is not toxic to acutely gavaged mice. Journal of Nutrition 126:728-740.

[8] Monsanto and KWS Petition to U.S. FDA. 2003. Safety, Compositional and Nutritional Assessment of Roundup Ready® Sugar beet Event H7-1. Monsanto Document #03-SB-094F. Monsanto Company, St. Louis, Missouri and KWS SAAT AG, Einbeck, Germany. Part VI Section 1 (Page 49), Section 3 (Pages 52-53), Section 5.3 (Page 60).

[9] Herrmann, K.M. 1995. The shikimate pathway: Early steps in the biosynthesis of aromatic compounds. The Plant Cell 7:907-919.

[10] Klee, H.J., Y.M. Muskopf, and C.S. Gasser. 1987. Cloning of an Arabidopsis thaliana gene encoding 5-enolpyruvylshikimate- 3-phosphate synthase: Sequence analysis and manipulation to obtain glyphosate-tolerant plants. Molecular and General Genetics 210:437-442.

[11] Monsanto and KWS Petition to U.S. FDA. 2003. Safety, Compositional and Nutritional Assessment of Roundup Ready® Sugar beet Event H7-1. Monsanto Document #03-SB-094F. Monsanto Company, St. Louis, Missouri and KWS SAAT AG, Einbeck, Germany. Part VI Sections 5.4-5.5 (Page 61).

[12] Padgette, S.R., D.B. Re, G.F. Barry, D.E. Eichholtz, X. Delannay, R.L. Fuchs, G.M. Kishore and R.T. Fraley. 1996. New weed control opportunities: Development of soybeans with a Roundup Ready™ gene. Pages 53-84 in Herbicide-Resistant Crops: Agricultural, Environmental, Economic, Regulatory, and Technical Aspects. S.O. Duke (ed.). CRC Press, Inc., Boca Raton, Florida.

[13] Monsanto and KWS Petition to U.S. FDA. 2003. Safety, Compositional and Nutritional Assessment of Roundup Ready® Sugar beet Event H7-1. Monsanto Document #03-SB-094F. Monsanto Company, St. Louis, Missouri and KWS SAAT AG, Einbeck, Germany. Part IV Section 2 (Page 22).

[14] Monsanto and KWS Petition to U.S. FDA. 2003. Safety, Compositional and Nutritional Assessment of Roundup Ready® Sugar beet Event H7-1. Monsanto Document #03-SB-094F. Monsanto Company, St. Louis, Missouri and KWS SAAT AG, Einbeck, Germany. Part IV Section 3.2a-b (Pages 27-30).

[15] Kraus, J. 2000. Molecular Analysis of Roundup Ready® Sugar beet Event H7-1. PLT6016-1MA. Einbeck, Germany. Confidential Business Information

[16] Hileman, R.E., K. Skottke and A. Silvanovich. 2019. Updated Bioinformatics Evaluation of H7-1 Sugar beet Utilizing the AD_2018, TOX_2018, PRT_2018, EST_2018, NT_2018, and NR_2018 Databases. Monsanto Technical Report RAR-2018-0333. St. Louis, Missouri. Confidential Business Information.

[17] Monsanto and KWS SAAT Ag. 2003. Safety Compositional and Nutritional Assessment of Roundup Ready Sugar beet Event H7-1. Monsanto #03-SB-094F Monsanto Company 709 Chesterfield Parkway North, St Louis, MO and KWSAAT AG Einbeck, Germany, Park VI Sections 2 (page 56)

[18] Leach, J.N., R.E. Hileman, J.J. Thorp, C. George and J.D. Astwood. 2002. Assessment of the in vitro Digestibility of Purified *E. coli*-produced CP4 EPSPS Protein in Simulated Gastric Fluid. Monsanto Technical Report MSL0017566. St. Louis, Missouri.

[19] Hernan, R., B. Chen, E. Bell, and J. Finnessy. 2011. Amended Report for MSL0022432: Effect of Temperature Treatment on the Functional Activity of CP4 EPSPS. Monsanto Technical Report MSL0023307. St. Louis, Missouri.

[20] Hernan, R., B. Chen, E. Bell, and J. Finnessy. 2011. Amended Report for MSL0022432: Effect of Temperature Treatment on the Functional Activity of CP4 EPSPS. Monsanto Technical Report MSL0023307. St. Louis, Missouri.

[21] Monsanto and KWS Petition to U.S. FDA. 2003. Safety, Compositional and Nutritional Assessment of Roundup Ready Sugar beet Event H7-1. Monsanto Document #03-SB-094F. Monsanto Company, St. Louis, Missouri and KWS SAAT AG, Einbeck, Germany. Part VI Section 5.2 (Page 60).

[22] Naylor, M. W. 1993. Acute Oral Toxicity Study of CP4 EPSPS Protein in Albino Mice. Monsanto Technical Report MSL-13077. St. Louis, Missouri.

[23] Lee, T.C., C.L. Mikols and J.D. Astwood. 2000. Assessment of the Physicochemical Equivalence of CP4 EPSPS Protein Produced in *Escherichia coli* and in Roundup Ready® Sugar beet Line H7-1. Monsanto Technical Report MSL-16579. St. Louis, Missouri.

[24] Monsanto and KWS Petition to U.S. FDA. 2003. Safety, Compositional and Nutritional Assessment of Roundup Ready® Sugar beet Event H7-1. Monsanto Document #03-SB-094F. Monsanto Company, St. Louis, Missouri and KWS SAAT AG, Einbeck, Germany. Part VI Section 1 (Pages 49-50).

[25] Monsanto and KWS Petition to U.S. FDA. 2003. Safety, Compositional and Nutritional Assessment of Roundup Ready® Sugar beet Event H7-1. Monsanto Document #03-SB-

094F. Monsanto Company, St. Louis, Missouri and KWS SAAT AG, Einbeck, Germany. Part VI Section 4 (Page 53).

[26] Silvanovich, A., N. Bhakta and T.C. Lee. 2003. Estimation of the Levels of CP4 EPSPS Protein in Beet Root Tissue and in Sugar, Molasses, and Pulp Processed Fractions Derived from Roundup Ready Sugar beet, Event H7-1. Monsanto Technical Report MSL-18848. St. Louis, Missouri.

[27] Klein, J., J. Altenbuchner and R. Mattes. 1998. Nucleic acid and protein elimination during the sugar manufacturing process of conventional and transgenic Sugar beets. Journal of Biotechnology 60:145-153.

[28] Delforge, S. 2001. Compositional Analyses of Roundup Ready® Sugar beet Event H7-1 from 1999 European Field Trials. AGREN 27.10.99. Vennecy, France.

[29] Monsanto and KWS Petition to U.S. FDA. 2003. Safety, Compositional and Nutritional Assessment of Roundup Ready® Sugar beet Event H7-1. Monsanto Document #03-SB-094F. Monsanto Company, St. Louis, Missouri and KWS SAAT AG, Einbeck, Germany. Part VI Section 3 (Pages 67-74).

[30] Morishita DW. 2016. Impact of glyphosate-resistant Sugar beet Science Published in Wiley Online Library: 6 February 2017 wileyonlinelibrary.com. DOI 10.1002/ps.4503

[31] Klein J, Altenbuchner J and Mattes, R, 1998. Nucleic acid and protein elimination during the sugar manufacturing process of conventional and transgenic Sugarbeets. J Biotechnol. 60:145–153.

[32] Kniss AR, 2010. Comparison of conventional and glyphosate-resistant Sugar beet the year of commercial introduction in Wyoming. J Am Soc Sugar beet Technol 47:127–134.

[33] Monsanto and KWS Petition to U.S. FDA. 2003. Safety, Compositional and Nutritional Assessment of Roundup Ready® Sugar beet Event H7-1. Monsanto Document #03-SB-094F. Monsanto Company, St. Louis, Missouri and KWS SAAT AG, Einbeck, Germany. Part VI Section 4.2 (Pages 55-58).

[34] Monsanto and KWS Petition to U.S. FDA. 2003. Safety, Compositional and Nutritional Assessment of Roundup Ready® Sugar beet Event H7-1. Monsanto Document #03-SB-094F. Monsanto Company, St. Louis, Missouri and KWS SAAT AG, Einbeck, Germany. Part VI Section 5.1 (Page 59).

[35] Rice, E.A., R.E. Goodman, A. Silvanovich, R.E. Hileman and J.D. Astwood. 2001. Bioinformatics Analysis of the CP4 EPSPS Utilizing ALLERGEN3 and Current Public Domain Sequence Databases. Monsanto Technical Report MSL-17172. St. Louis, Missouri. Confidential Business Information

[36] BLAST: https://blast.ncbi.nlm.nih.gov/Blast.cgi

[37] Pearson, W.R. and Lipman, D.J. 1988. Improved tools for biological sequence comparison. Proceedings of the National Academy of Sciences of the United States of America 85:2444-2448.

[38] Harrison, L.A., M.R. Bailey, M.W. Naylor, J.E. Ream B.G. Hammond, D.L. Nida, B.L. Burnette, T.E. Nickson, A. Mitsky, M.L. Taylor, R.L. Fuchs and S.R. Padgette. 1996. The expressed protein in glyphosate-tolerant soybean, 5-enolypyruvylshikimate-3-phosphate synthase from *Agrobacterium* sp. strain CP4, is rapidly digested in vitro and is not toxic to acutely gavaged mice.

[39] Smed, E., A.W.M. Huijbregts, D. Hadjiantoniou and G. Vallini. 1996. Influence of agronomic factors on non-conventional parameters of the internal quality of Sugar beet. Pages 385-389 in Proceedings of the 59th IIRB Congress, Brussels, Belgium.

[40] Fuchs, R., Ream, J., Hammond, B., Naylor, M., Leimgruber, R., & Berberich, S. (1993). Safety Assessment of the Neomycin Phosphotransferase II (NPT II) Protein. Bio/Technology Bulletin, 11:1543- 172.