RISK ASSESSMENT REPORT

OF THE GENETIC MODIFICATION ADVISORY COMMITTEE (GMAC)

FOR

AN APPLICATION FOR APPROVAL FOR RELEASE OF PRODUCTS OF

HB4 SOYBEAN FOR SUPPLY OR OFFER TO SUPPLY

NBB REF NO: JBK(S) 600-2/1/20

APPLICANT: INSTITUTO DE AGROBIOTECNOLOGIA ROSARIO

DATE: 22 JUNE 2022

I - Summary of Assessment Process

On 18 February 2022, the Genetic Modification Advisory Committee (GMAC), received from the Department of Biosafety an application for the approval for importation for release [sale/placing on the market for direct use as food, feed and for processing (FFP)] of a product of a Living Modified Organism abiotic stress and herbicide tolerant HB4 soybean. The application was filed by Instituto de Agrobiotecnologia Rosario (hereafter referred to as "the applicant"). After an initial review, GMAC requested for additional information from the applicant.

A public consultation for this application was conducted from 20 October 2021 to 18 November 2021 via advertisements in the local newspapers, e-mail announcements and social media. Comments were received from Consumers Association of Penang (CAP) and Malaysian Palm Oil Board (MPOB). GMAC took into consideration comments that were relevant to the risk assessment including safety of the expressed HAHB4 protein, glufosinate residue, unintentional release and the requirement for labelling.

GMAC had four (4) meetings pertaining to this application and prepared the Risk Assessment Report and Risk Assessment Matrix along with its recommended decision, for consideration by the National Biosafety Board.

II - Background of Application

This application is for approval to import and release products of a Living Modified Organism HB4 soybean. The aim of the import and release is to supply or offer to supply for sale/placing on the market for direct use as food, feed and for processing (FFP). According to the applicant, HB4 soybean has been registered in a number of countries for cultivation as well as for food, feed and for processing. HB4 soybean is approved in the Argentina, Brazil, Canada and United States of America and may be imported, stored and processed for use in food, animal feed and industrial products in the same way as other conventional, non-transgenic soybean. The type of expected use of the products derived from HB4 soybean in Malaysia will be the same as the expected usage for products derived from conventional soybean. This application does not cover environmental release and HB4 soybean may be imported to Malaysia as food or feed products or for further processing.

Information about HB4 soybean

The recipient or parental plant is *Glycine max* (soybean). Soybean has a long history of domestication and consumption by humans, and foods containing soybean-derived products are consumed by a large proportion of the global population. (Liu, 2004).

HB4 soybean was developed via *Agrobacterium tumefaciens*-mediated transformation of conventional soybean with the introduction of two genes, the *HaHB4* gene, conferring tolerance to water deficit, and the *bar* gene providing the crop with tolerance to glufosinate herbicides. The

HaHB4 gene is derived from the sunflower plant and expresses the HAHB4 protein, a plant transcription factor that regulates the plant response to environmental stress. The presence of HAHB4 protein allows HB4 soybean to keep productive processes active under water deficit conditions, rendering higher yield. The *bar* gene, derived from the soil bacteria *Streptomyces hygroscopicus,* codes for the phosphinothricin-N-acetyltransferase (PAT) enzyme, which inactivates the active principle in glufosinate-based herbicides, conferring tolerance to the herbicide glufosinate.

III - Risk Assessment and Risk Management Plan

GMAC evaluated the application with reference to the following documents:

(i) CODEX Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants**.**

(ii) Roadmap for Risk Assessment of Living Modified Organisms, (according to Annex III of the Cartagena Protocol on Biosafety produced by the *Ad Hoc* Technical Expert Group (AHTEG) on Risk Assessment and Risk Management of the Convention on Biological Diversity).

(iii) The risk assessment and risk management plan submitted by the applicant.

GMAC also referred to the following recommendations within the AHTEG guidelines:

(i) That the risk assessment exercise be specific to the details of this particular application

(ii) That the risk assessment exercise be specific to the receiving environment in question, and

(iii) That any risk identified be compared against that posed by the unmodified organism.

In conducting the risk assessment, GMAC identified potential hazards, and then added a value/rank for the likelihood of each hazard as well as its consequences. The likelihood of each hazard occurring was evaluated qualitatively on a scale of 1 to 4, with 1 for 'highly unlikely', and 4 for 'highly likely'. The consequences of each hazard, if it were to occur, were then evaluated on a scale of 1 to 4, with 1 for 'marginal' and 4 to denote a 'major consequence'. A value was finally assigned for the overall risk from the identified potential hazard. The general formula: Overall Risk = Likelihood x Consequence was employed. GMAC also proposed risk management strategies for potential hazards, where appropriate. This methodology of assessment follows the procedure of Risk Assessment in Annex III of the Cartagena Protocol on Biosafety.

The potential hazards were identified in three main areas:

(i) **<u>Effects on human health</u>**

Relevant scientific publications on the genetic modifications were reviewed for potential human health risks and issues pertaining to acute toxicity of novel protein /

altering / interference of metabolic pathways, potential allergenicity of the novel protein, reproductive toxicity, potential transfer of antibiotic resistance genes in digestive tract, pathogenic potential of donor microorganisms, nutritional equivalence and anti-nutritional properties.

(ii) **Effects on animal health**

Relevant scientific publications on the genetic modifications were reviewed for potential animal health risks and issues pertaining to allergenicity, toxicity, anti-nutritional components, survivability, and animal product contamination.

(iii) **Effects on the environment**

Relevant scientific publications on the genetic modifications were reviewed for potential environmental risks and issues pertaining to accidental release of seeds, unintentional release and planting, weediness and invasiveness, increased fitness due to genetic modification, potential of transgenes being transferred to bacteria (soil bacteria, bacterial flora of animal gut), accumulation of the proteins in the environment via feces from animals fed with the GM plant/grain and cross pollination leading to transfer of transgenes.

Based on the above, a final list of 20 potential hazards was identified. Most of these hazards were rated as having an Overall Risk of 1 or “negligible”.

GMAC also took caution and discussed a few of the hazards that required further evaluation and data acquisition. Some of these risks are expected to be managed effectively with the risk management strategies proposed (please refer to section IV of this document).

Some of the potential hazards are highlighted below along with the appropriate management strategies:

a) Accidental release of viable seeds

Seeds may be accidentally released during transportation. These seeds can germinate and grow along transportation routes and in areas surrounding storage and processing facilities. Any spillage shall be collected and cleaned up immediately. Transportation of the consignment must be in secured and closed conditions. Soybean is not grown as an economic crop in Malaysia, thus, there is no issue of outcrossing.

b) Planting of seeds

Plants may be grown by uninformed farmers and perpetuated through small scale cultivations. There should also be clear labeling of the product to state that it is only for the purpose of food, feed and processing, and is not to be used as planting material.

c) Nutritional equivalence

The compositional analysis of HB4 soybean and controlled soybean showed six statistically significant differences in stearic acid, oleic acid, arachidic acid, vitamin K1, daidzein, and glycitein. However, in all cases, the differences were small, and the analyte levels were within the references ranges observed for commercial soybean varieties. Therefore, the nutritional quality of HB4 soybean is comparable to conventional soybean varieties which are currently safely grown and consumed.

However, applicant is required to update the National Biosafety Board immediately if additional tests indicate potential adverse effects or the possible presence of toxin or allergenic proteins.

IV - Proposed Terms and Conditions for Certificate of Approval

Based on the 20 potential hazards identified and assessed, GMAC has drawn up the following terms and conditions to be included in the certificate of approval for the release of this product:

a) There shall be clear documentation by the exporter describing the product which shall be declared to the Royal Malaysian Customs.

b) There shall be clear labeling of the product from importation to all levels of marketing stating that it is only for the purpose of food, feed and processing, and is not to be used as planting material.

c) Should the approved person receive any credible and/or scientifically proven information that indicates any adverse effect of HB4 soybean, the National Biosafety Board shall be informed immediately.

d) Any spillage (during loading/unloading/transportation) shall be collected and cleaned up immediately.

e) Transportation of the consignment from the port of entry to any destination within the country shall be in secured and closed condition.

f) Any import or release of products derived from any new genetically modified lines bred using HB4 soybean will require a separate approval from the National Biosafety Board.

V - Other Regulatory Considerations

a) Administrative regulatory procedures shall be arranged between the Department of Biosafety, Royal Malaysian Customs Department and relevant agencies to ensure accurate declaration of product information and clear labeling of the product is implemented.

b) Administrative regulatory procedures shall be arranged between the Department of Biosafety and the Malaysian Quarantine and Inspection Services (MAQIS) to impose post entry requirements for accidental spillage involving the GM product.

c) Administrative regulatory procedures shall be arranged between the Department of Biosafety and the Malaysian Quarantine and Inspection Services (MAQIS) and other competent agencies to impose post entry requirements for food safety compliance.

d) Administrative regulatory arrangements shall be carried out between the Department of Biosafety and the Department of Veterinary Services (DVS) so that any unanticipated adverse effects in animals caused by any consumption of the GM products shall be reported immediately.

e) Administrative regulatory arrangements shall be carried out by Food Safety and Quality of Ministry of Health to monitor compliance to the Food Act 1983 and Food Regulations 1985; and GM food labelling guidelines.

f) Administrative regulatory procedures shall be arranged between Department of Biosafety and Ministry of Health to ensure that herbicide residues in soybean consignments are below the maximum residual level established. It is recommended that importers are required to provide certificate of analysis for herbicide residues prior to shipment.

VI - Identification of issues to be addressed for long term use release of this product

a) Continuous monitoring is required from the approved person and any unanticipated adverse effect caused by the HB4 soybean shall be reported to the National Biosafety Board.

VII –Conclusion and Recommendation

GMAC has conducted a thorough evaluation of the application for approval for importation for release [sale/placing on the market for direct use as food, feed and for processing (FFP)] of a product of a Living Modified Organism, abiotic stress and herbicide tolerant HB4 soybean and has determined that the release of this product does not endanger biological diversity or human, animal and plant health. GMAC recommends that the proposed application for release be **APPROVED WITH TERMS AND CONDITIONS** as listed in section IV - Proposed Terms and Conditions for Certificate of Approval.

VIII - Bibliography

1. Bultman J (2019). A 90-Day Oral (Dietary) Toxicity Study of Transgenic Soybean Meal from IND-ØØ41Ø-5 in Sprague Dawley Rats. Charles River Laboratory Project ID: 01020001. 1544 pp.
2. Burachik, M., Ferelan, A. & Miranda, P. (2019). 90-Day Oral Toxicity Study of IND-ØØ41Ø-5 Soybean. INDEAR Technical Report #01010307-Ev2 IND-ØØ41Ø-5 Soybean.
3. CERA (2011) A review of the environmental safety of the PAT protein. Center for Environmental Risk Assessment, ILSI Research Foundation. Environ Biosafety Res 10:73–101
4. Crawley, M.J., S.L. Brown, R.S. Hails, D.D. Koh and M. Rees. 2001. Transgenic crops in natural habitats. Nature 409:682-683.
5. de Alencar, E.R., L.R.D.A. Faroni, A.F. de Lacerda Filho, L.G. Ferreira and M.R. Meneghitti. 2006. Influence of different storage conditions on soybean grain quality. Pages 30-37 in 9th International Working Conference on Stored Product Protection, Campinas, São Paulo, Brazil.
6. FAO-WHO. 2001. Evaluation of allergenicity of genetically modified foods. Report of a joint FAO/WHO expert consultation on allergenicity of foods derived from biotechnology. Food and Agriculture Organization of the United Nations, Rome, Italy.
7. Fazio, G., Ferela A, Miranda PV (2020). Assessment of HAHB4 Protein Safety. INDEAR Report ID: 01010273-Ev2. 28 pp.
8. Hérouet C, Esdaile DJ, Mallyon BA, Debruyne E, Schulz A, Currier T, Hendrickx K, van der Klis RJ, Rouan D.(2005) Safety evaluation of the phosphinothricin acetyltransferase proteins encoded by the pat and bar sequences that confer tolerance to glufosinate-ammonium herbicide in transgenic plants. Regul Toxicol Pharmacol. 2005 Mar;41(2):134-49. doi: 10.1016/j.yrtph.2004.11.002. Epub 2005 Jan 18. PMID: 15698537.
9. Inspecting and Testing Center of Genetically Modified Food Safety (2017). HAHB4 Acute Oral Toxicity Study. Testing Center of Genetically Modified Food Safety, Chinese Agricultural University.
10. ILSI (2016). A Review of the Food and Feed Safety of the PAT Protein. ILSI Research Foundation. Washington, D.C. USA.
11. Ivashuta, S.I., J.S. Petrick, S.E. Heisel, Y. Zhang, L. Guo, T.L. Reynolds, J.F. Rice, E. Allen and J.K. Roberts. 2009. Endogenous small RNAs in grain: Semi-quantification and sequence homology to human and animal genes. Food and Chemical Toxicology 47:353-360.
12. Jensen, P.D., Y. Zhang, B.E. Wiggins, J.S. Petrick, J. Zhu, R.A. Kerstetter, G.R. Heck and S.I. Ivashuta. 2013. Computational sequence analysis of predicted long dsRNA transcriptomes of major crops reveals sequence complementarity with human genes. GM Crops and Food 4:90-97.
13. Liu, K. 2004. Soybeans as Functional Foods and Ingredients (1st ed.). AOCS Publishing. https://doi.org/10.1201/9781003040286
14. Lusas, E.W. 2004. Soybean processing and utilization. Pages 949-1045 in Soybeans: Improvement, Production, and Uses. Third Edition. H.R. Boerma and J.E. Specht (eds.).

American Society of Agronomy, Inc., Crop Science Society of America, Inc., Soil Science Society of America, Inc., Madison, Wisconsin.
15. Mbofung, G.C.Y., A.S. Goggi, L.F.S. Leandro and R.E. Mullen. 2013. Effects of storage temperature and relative humidity on viability and vigor of treated soybean seeds. Crop Science 53: 1086–1095.
16. Owen, M.D.K. 2005. Maize and soybeans—Controllable volunteerism without ferality? Pages 149-165 in Crop Ferality and Volunteerism. J. Gressel (ed.) Taylor & Francis, Boca Raton, Florida.
17. OECD. 2000. Consensus document on the biology of Glycine max (L.) Merr. (Soybean). ENV/JM/MONO(2000)9. Series on Harmonization of Regulatory Oversight in Biotechnology No.15. Organisation for Economic Co-operation and Development, Paris, France.
18. OECD (2012). Revised consensus document on compositional considerations for new Varieties of soybean [Glycine max (L.) Merr.]: key food and feed nutrients, anti-nutrients, toxicants and allergens. Document ENV/JM/MONO(2012)24. Organization for Economic Development and Cooperation. Paris, France.
19. Petrick, J.S., B. Brower-Toland, A.L. Jackson and L.D. Kier. 2013. Safety assessment of food and feed from biotechnology-derived crops employing RNA-mediated gene regulation to achieve desired traits: A scientific review. Regulatory Toxicology and Pharmacology 66:167-176.
20. Revale S, Ferela A and Miranda P (2020). Bioinformatic Analysis of Soybean Event IND-ØØ41Ø-5. INDEAR Report ID: 291 V4. 43 pp.
21. Ricroch AE, Berge JB and Kuntz M (2011). Evaluation of genetically engineered crops using transcriptomic, proteomic and metabolomic profiling techniques. Plant Physiol. 155, 1752 1761.
22. Roberts, A., Y. Devos, A. Raybould, P. Bigelow and A. Gray. 2014. Environmental risk assessment of GE plants under low-exposure conditions. Transgenic Research 23:971-983.
23. Singh RJ (2017). Botany and Cytogenetics of Soybean. In The Soybean Genome, Compendium of Plant Genomes. Chapter 2, pp. 11-40. H.T. Nguyen and M.K. (Eds)
24. Skinner, W. & Fazio, G. (2016). HAHB4 Protein Detection IND-ØØ41Ø-5 Soybean. INDEAR Technical Report #0000273
25. Skinner, W. & Fazio, G. (2016). PAT Protein Detection in Field-Grown Seed and Leaves from IND-ØØ41Ø-5 soybean. INDEAR Technical Report #1010297
26. Taylor SL, Nordlee JA, Sicherer SH et al. (2004). Soybean oil is not allergenic to soybeanallergic individuals. J. Aller. Clin. Immunol., 113(2), Supplement: S99.
27. U.S. FDA. 1992. Statement of policy: Foods derived from new plant varieties. Federal Register 57:22984-23005.
28. U.S. FDA. 2001. Premarket notice concerning bioengineered foods. Federal Register 66:4706-4738.
29. Verhoeckx KCM, Vissers YM, Baumert JL, Faludi R, Feys M, Flanagan S, Herouet-Guicheney C, Holzhauser T, Shimojo R, van der Bolt N, Wichers H, Kimber I (2015). Food processing and allergenicity. Food Chem Toxicol 80:223-240. doi: 10.1016/j.fct.2015.03.005. Epub 2015 Mar 14.

Appendix 1

GENETIC MODIFICATION ADVISORY COMMITTEE (GMAC) MEMBERS INVOLVED IN SPECIFIC RISK ASSESSMENT AREAS FOR THE APPROVAL FOR RELEASE OF PRODUCTS OF HB4 SOYBEAN FOR SUPPLY OR OFFER TO SUPPLY

Genetic Modification Advisory Committee (GMAC) members divided the task of looking up more information for the Risk Assessment matrix based on three broad categories which were environment, human health and animal health. Each sub-committee had a nominated leader to coordinate the work and report back to the main GMAC. The GMAC members involved in the risk assessment are as below:

1. **Prof. Dr. Mohd. Faiz Foong bin Abdullah (Universiti Teknologi MARA) (GMAC Chairman)**
2. **Dr. Kodi Isparan Kandasamy (Industry Representative) (Environment sub-committee Leader)**
3. **Madam T.S. Saraswathy (Institute of Medical Research - retired) (Human Health sub-committee Leader)**
4. **Prof. Dr Jothi Malar Panandam (Universiti Putra Malaysia - retired) (Animal Health sub-committee Leader)**
5. **Dr. Rahizan Issa (Institute of Medical Research - retired) (Notification Assessment sub-committee Leader)**
6. Dato' Dr. Sim Soon Liang (Academy of Sciences Malaysia)
7. Prof. Dr. Chan Kok Gan (Universiti Malaya)
8. Assoc. Prof. Dr. Choong Chee Yen (Universiti Kebangsaan Malaysia)
9. Dr. Adiratna Mat Ripen (Institute of Medical Research)
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11. Dr. Norwati Muhammad (Forest Research Institute of Malaysia)
12. Dr. Saifullizam bin Abdul Kadir (Department of Veterinary Services)
13. Dr. Teo Tze Min (Entomological Society of Malaysia)
14. Dr. Mohd Hefni Rusli (Malaysian Palm Oil Board)
15. Madam Shafini Abu Bakar (Ministry of Health)
16. Madam Sabariah Kamis (Department of Agriculture)
17. Mr. Harun bin Ahmad (Department of Chemistry Malaysia)
18. Assoc. Prof. Dr. Sharifah binti Syed Hassan (Monash University Malaysia)
19. Dr. Kumitaa Theva Das (Universiti Sains Malaysia)