FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR VETERINARY MEDICINE

Biotechnology Notification File No. 000205
CVM Note to the File

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From: Jing Ning, Ph.D.

To: Administrative Record, BNF No. 000205

Subject: Event Kal91.3 Potato

Keywords: Potato, *Solanum tuberosum* subsp. *tuberosum*, RNA interference (RNAi), *VInv* gene, Lower reducing sugars, *neomycin phosphotransferase II* (*nptII*) gene, *Escherichia coli*, Michigan State University, Kal91.3.

Purpose

This document summarizes the Food and Drug Administration (FDA) Center for Veterinary Medicine's (CVM, we) evaluation of biotechnology notification file (BNF) number 000205. The Michigan State University (MSU) submitted a safety and nutritional assessment for a genetically engineered (GE) potato, transformation event Kal91.3(hereafter referred to as Kal91.3 potato), and additional information afterwards. We evaluated the information in MSU's submissions to ensure that regulatory and safety issues regarding animal food derived from Kal91.3 potato have been resolved prior to commercial distribution. FDA's Human Foods Program (HFP) summarizes its evaluation of uses of Kal91.3 potato in human food in a separate document.

In CVM's evaluation, we considered all of the information provided by MSU as well as publicly available information and information in the agency's files. Here we discuss the outcome of the consultation for animal food use, but do not intend to restate the information provided in the final consultation in its entirety.

Intended Effects

The intended effect of the modification in Kal91.3 potato is to lower levels of reducing sugars. MSU introduced DNA sequences containing inverted repeat segments of *vacuolar invertase* gene (*VInv*), which produce dsRNA to reduce RNA transcript levels of *VInv*. *VInv* gene encodes the VInv protein which participates in converting sucrose to its component reducing sugars. MSU also introduced the *neomycin phosphotransferase II* (*nptII*) gene from *Escherichia coli* that encodes for NPTII protein which serves as a selectable marker.

Regulatory Considerations

The purposes of this evaluation are (1) to assess whether MSU has introduced into animal food a substance requiring premarket approval as a food additive and (2) to determine whether use of the new plant variety in animal food raises other regulatory issues with respect to the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Genetic Modification and Characterization

Introduced DNA and Transformation Method

MSU transformed internode explants obtained from a potato variety Kalkaska with plasmid pINVBP1 using disarmed *Agrobacterium tumefaciens* mediated transformation.[1] The transfer-DNA (T-DNA) region within plasmid pINVBP1 contains the following two expression cassettes between left and right border sequences:

- A partial sequence of the *VInv* gene from *S.tuberosum*, and a spacer sequence, followed by the complementary partial sequence of *VInv* in reverse orientation. The cassette is preceded by the *CaMV 35S* promoter. When transcribed, this cassette generates dsRNA with partial sequence of *VInv*.
- *nptII* gene from *E.coli*, which is preceded by the *NOS* promoter and followed by NOS terminator.

Following transformation, explants were grown in kanamycin selection medium to select for T-DNA. Regenerated plantlets were used in the characterization of insert number, insert integrity and absence of vector backbone sequences.

MSU used a combination of techniques, including whole genome sequencing (WGS), droplet digital PCR (ddPCR), polymerase chain reaction (PCR), Southern blot and Sanger sequencing to characterize the insertion event in Kal91.3 potato. The parental variety, Kalkaska, was used as the comparator in these analyses. MSU reports that two T-DNA sequences were inserted into the Kal91.3 potato genome and that backbone sequences from pINVBP1 were not present in Kal91.3 potato. WGS and Sanger sequencing demonstrated that the transformation introduced a 454bp and 323bp truncation at the left border of each T-DNA insertion. MSU stated that the genetic modification does not interrupt or delete any genes.

The stability of the inserted T-DNA sequences in Kal91.3 potato was assessed using PCR in plants that had undergone successive rounds of vegetative propagation. Four targeted regions were assessed by PCR to detect the T-DNA insertion sites. MSU states that PCR analysis confirmed the stability of two T-DNA inserts in Kal91.3 potato across three rounds of vegetative propagation.

MSU performed bioinformatics analyses using sequences obtained for two T-DNA inserts and flanking sequences to determine whether insertion of the introduced DNA created any potential open reading frames (ORF) that could encode putative polypeptides. MSU utilized the NCBI and UniProtKB/Swiss-Prot database to determine

[1] Douches, D.S., A.L. Westedt, K. A. Zarka, and E.J. Grafius. 1998. Transformation of CryV-Bt transgene combined with natural resistance mechanisms for resistance to tuber moth in potato (Solanum tuberosum L.) HortScience 33(6):1053-1056.

the similarity of the putative polypeptides to known toxins. MSU concludes that the T-DNA insertions do not lead to the production of putative polypeptides that would raise animal food safety concerns.

Intended Effects: Reduced Levels of Specific RNA Transcripts in Tubers

To characterize the level of the *Vlnv* transcript targeted by the gene silencing construct, RNA isolated from tubers obtained from Kal91.3 and control potato were analyzed with the NanoString nCounter system. MSU reported reduction in RNA transcript for the *VInv* gene in Kal91.3 potato tubers when compared to control tubers.[2]

Protein Safety

Kal91.3 potato was genetically engineered to express NPTII derived from *E. coli*. NPTII confers resistance to neomycin and kanamycin and serves as a selectable marker for Kal91.3 potato transformation. MSU states that the NPTII protein in Kal91.3 potato is identical to NPTII protein expressed in several GE plant varieties that have completed FDA's consultation program[3]. MSU also summarizes scientific literatures to support the safety of the NPTII protein in GE plant varieties. MSU quantified NPTII protein level in tuber using Enzyme-linked immunosorbent assay (ELISA). MSU states that NPTII protein level in Kal91.3 potato did not exceed the amount observed in previously evaluated GE plant varieties and the protein was expressed at no more 0.6 micrograms/gram in tuber in Kal91.3 potato.

Based on the history of safe use of the introduced proteins in other plant varieties and the information discussed above, MSU concludes that NPTII protein expressed in Kal91.3 potato is safe when used in animal food.

Animal Food Use

MSU states that Kal91.3 potato is expected to be grown for the same uses as currently commercialized potatoes. The typical uses of potato-derived food and feed are well documented in Organisation for Economic Co-operation and Development (OECD) potato composition consensus document,[4] including use of potato peels, out of specification potatoes, unprocessed raw potatoes, and processed discards from cooked potatoes for animal food.

Composition

Scope of Analysis

MSU conducted compositional analyses on tubers obtained from Kal91.3 potato and the non-GE control variety, Kalkaska (control).

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[2] MSU reports that Kal91.3 potato chips have a lighter color compared to Kalkaska potato chips after 6 months and 8 months of storage at cold temperature.

[3] MSU notes that NPTII protein produced in Kal91.3 potato is identical to the NPTII protein expressed in MON 87460 corn (BNF No. 000116), MON 15985 cotton (BNF No. 000074), MON 863 corn (BNF No. 00074) and MON 531 cotton (BNF No. 000013), and MON 1445 cotton (BNF No. 000026).

[4] Organisation for Economic Co-operation and Development. 2021. Revised consensus document on compositional considerations for new varieties of potato (*Solanum tuberosum*): Key food and feed nutrients, toxicants, allergens, anti-nutrients, and other secondary metabolites. Series on the safety of novel foods and feeds No. 33. ENV/JM/MONO. OECD, Paris.

Study Design

MSU grew Kal91.3 potato and control in the United States in 2023 and 2024. A randomized complete block design with four replicate plots was used. MSU presents mean values, range of values and results of the statistical comparison of Kal91.3 potato and control. MSU also presents ranges obtained from public databases or scientific literatures for each component (hereafter referred to as combined literature range).[5]

Results of Analyses

MSU reports values for proximates (protein, total fat, carbohydrates by calculation, and ash), total dietary fiber (TDF), two vitamins (vitamin D2 and D3), potassium, sucrose, fructose, glucose and total glycoalkaloids (alpha-solanine and alpha-chaconine). MSU reported no statistically significant differences for each of these components between Kal91.3 potato and control. MSU notes that the mean values of total glycoalkaloids in Kal91.3 potato and control fell within the combined literature range. MSU concludes that Kal91.3 potato is compositionally comparable to control potato.

Summary of Compositional Analyses

MSU states that Kal91.3 potato is compositionally equivalent to control potato variety, and Kal91.3 potato is as safe and nutritious for use in animal food as conventional potato varieties that have a long history of safe use in animal food.

Conclusion

CVM evaluated MSU's submissions to determine whether Kal91.3 potato raises any safety or regulatory issues with respect to its use in animal food. Based on the information provided by MSU and other information available to the agency, CVM did not identify any safety or regulatory issues under the FD&C Act that would require further evaluation at this time.

MSU concludes that Kal91.3 potato and the animal foods derived from it are as safe as and are not materially different in composition or any other relevant parameter from other potato varieties now grown, marketed, and consumed. At this time, based on MSU's data and information, CVM considers MSU's consultation on Kal91.3 potato for use in animal food to be complete.

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[5] MSU referred to potato data presented in Agriculture and Food Systems Institute (AFSI) Crop Composition Database at https://www.cropcomposition.org/CCDB/SelectAnalytes, OECD potato consensus document. For glycoalkaloids, MSU referred to Kozukue, N., Yoon, K.-S., Byun, G.-I., Misoo, S., Levin, C.E., Friedman, M., 2008. Distribution of glycoalkaloids in potato tubers of 59 accessions of two wild and five cultivated Solanum species. J Agric Food Chem 56, 11920–8. and AFSI (accessed 12/2025). For sucrose, fructose and glucose, MSU referred to Amrein et al 2003, Vivanti et al 2006 and AFSI Database 2025. Amrein, T.M., S. Bachmann, A. Noti, M. Biedermann, M.F. Barbosa, S. Biedermann-Brem, K. Grob, A. Keiser, P. Realini, F. Escher, R. Amado. 2003. Potential of acrylamide formation, sugars, and free asparagine in potatoes: A comparison of cultivars and farming systems. J. Agric. Food Chem. 51:5556-5560; Vivanti, V. E. Finotti, and M. Friedman. 2006. Level of acrylamide precursors asparagine, fructose, glucose, and sucrose in potatoes sold at retail in Italy and in the United States. J. Food Sci. 71:C81-C85.