U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

# Biotechnology Notification File No. 000199
# HFP Note to the File

**Date:** November 26, 2024

**From:** Charles Kanobe, Ph.D.

**To:** Administrative Record, BNF No. 000199

**Subject**: Soybean with transformation event MON 94637 (MON 94637 soybean)

**Keywords:** Soybean, Glycine max (L.) Merr., insect resistance, lepidoptera, cry1A.2 gene, Cry1A.2 protein, cry1B.2 gene, Cry1B.2 protein, Bacillus thuringiensis, Bayer CropScience LP., MON 94637, OECD unique identifier MON-94637-8

## Summary

Bayer CropScience LP. (Bayer) has completed a consultation with the Food and Drug Administration (FDA) on food derived from MON 94637 soybean genetically engineered to express Cry1A.2 and Cry1B.2 proteins from *Bacillus thuringiensis* to confer resistance to susceptible lepidopteran insects. During the development of MON 94637 soybean, Bayer used the splA protein from *Agrobacterium tumefaciens* and the aadA protein from *E. coli* transposon Tn7 as selection markers that were subsequently segregated out to ensure that the final product contained only *cry1A.2* and *cry1B.2* expression cassettes. This document summarizes Bayer's conclusions and supporting data and information that FDA's Human Foods Program (HFP, we) evaluated pertaining to human food uses of MON 94637 soybean. FDA's Center for Veterinary Medicine summarizes its evaluation pertaining to animal food uses in a separate document.

Based on the safety and nutritional assessment Bayer has conducted, it is our understanding that Bayer concludes:

- it has not introduced into human food a new protein or other substance that would require premarket approval as a food additive; and
- human food from MON 94637 soybean is comparable to and as safe as human food from other soybean varieties.

HFP evaluated data and information supporting these conclusions and considered whether MON 94637 soybean raises other regulatory issues involving human food within FDA's authority under the Federal Food, Drug, and Cosmetic Act (FD&C Act). We have no further questions at this time about the safety, nutrition, and regulatory compliance of human food from MON 94637 soybean.

The U.S. Environmental Protection Agency (EPA) evaluates and authorizes the use of plant incorporated protectants (PIPs) under the FD&C Act and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). A PIP is defined in 40 CFR 174.3 as "a pesticidal substance that is intended to be produced and used in a living plant, or the produce thereof, and the genetic material necessary for the production of such a pesticidal substance," including "any inert ingredient contained in the plant, or produce thereof." In MON 94637 soybean, the Cry1A.2 and Cry1B.2 proteins are PIPs. Bayer explained that it will seek an

exemption from the requirement of a tolerance for Cry1A.2 and Cry1B.2 in or on food derived from MON 94637 soybean. The safety of Cry1A.2 and Cry1B.2 in MON 94637 soybean falls under EPA's purview and therefore is not addressed in this document.

## Subject of the Consultation

| | |
|---|---|
| **Crop** | Soybean |
| **Designation** | MON 94637 |
| **Intended trait** | Insect resistance |
| **Developer** | Bayer CropScience LP. |
| **Submission received** | August 04, 2023 |
| **Amendments received** | February 16, 2024; June 19, 2024; July 08, 2024 |
| **Intended use** | General use in human food |
| **Transformation plasmid** | Plasmid PV-GMIR527237 |
| **Expression cassette 1**[1] | The *cry1A.2* gene cassette encodes the Cry1A.2 protein from *Bacillus thuringiensis*. It confers resistance to susceptible lepidopteran pests. |
| **Expression cassette 2**[1] | The *cry1B.2* gene cassette encodes the Cry1B.2 protein from *Bacillus thuringiensis*. It confers resistance to susceptible lepidopteran pests. |
| **Expression cassette 3**[2] | The *splA* gene cassette from *A. tumefaciens* encodes the sucrose phosphorylase protein that catalyzes the conversion of sucrose to fructose and glucose-1-phosphate. splA was used as a selectable marker. |
| **Expression cassette 4**[2] | The *aadA* gene cassette from *E. coli* transposon Tn7 encodes the 3"(9)-*O*-nucleotidyltransferase enzyme conferring resistance to spectinomycin and streptomycin. aadA was used as a selectable marker. |
| **Method for conferring genetic change** | *Agrobacterium*-mediated transformation |

## Inheritance and stability

MON 94637 soybean was developed from the conventional soybean variety A3555 transformed with the binary plasmid vector PV-GMIR527237 using *Agrobacterium*-mediated transformation. After transformation, soybean plantlets were regenerated and characterized using copy number assay and linkage analysis. Plants containing only T-DNA I (unlinked to T-DNA II), were selected and advanced for additional testing.

[1] The c*ry1A.2* and *cry1B.2* gene cassettes were contained on T-DNA I.
[2] The *splA* and *aadA* gene cassettes were contained on T-DNA II and were subsequently segregated out of MON 94637.

Bayer then performed whole genome sequencing on five breeding generations of MON 94637 soybean to determine the stability of the T-DNA I insert. Bayer reported two identical junctions present in all the breeding generations tested, thereby confirming the presence of a single T-DNA I insert stably maintained in subsequent generations. Therefore, Bayer concluded that the single copy of T-DNA I in MON 94637 soybean was stable and equivalent across multiple generations in the breeding process.

Bayer also studied inheritance of the MON 94637 trait in three generations of MON 94637 soybean. Segregation analysis results showed no statistically significant difference between the observed and expected segregation ratios of MON 94637 T-DNA I in the three generations studied. Bayer therefore concluded that MON 94637 T-DNA I is present as a single copy at a single locus and is inherited according to Mendelian principles of inheritance.

## Human Food Nutritional Assessment

The intended traits in MON 94637 soybean are not expected to alter levels of key nutrients or anti-nutrients. To assess potential unintended changes in composition relevant to safety or nutrition, Bayer analyzed grain from MON 94637 soybean and a non-genetically engineered (non-GE) control grown at five locations in the United States in 2021. In their analyses, Bayer followed considerations as defined by the OECD in their revised consensus document on compositional considerations for new varieties of soybean.[3] Grain samples were assessed for moisture, proximates, amino acids, fatty acids, carbohydrates (by calculation), fiber (ADF and NDF), minerals, vitamins, anti-nutrients (phytic acid, raffinose, soybean lectin, stachyose, and trypsin inhibitor) and isoflavones (daidzein, genistein, and glycitein). Analytical data means from MON 94637 soybean were compared to the range of means of the non-GE control across multiple study environments and ranges from publicly available literature and databases.[4] Comparing of results to literature ranges provides context for natural variation of plant composition resulting from a combination of genetic diversity and environmental conditions at time of production.

Bayer reported the results of its analysis, noting that eleven analytes had more than 50% of observations below the assay limit of quantitation and therefore were not statistically analyzed. Bayer reported that there were no statistically significant differences observed between MON 94637 soybean and the non-GE control for the remaining grain-derived analytes except for palmitoleic acid, heptadecanoic acid, and behenic acid. However, for these three analytes, the mean difference in component values between MON 94637 and the non-GE control was less than the range of non-GE control values. In addition, the MON 94637 mean component values for the analytes were within the range of values observed in literature and/or in the Agriculture and Food Systems Institute (AFSI) crop composition database.[4] Bayer explained that these results indicate that MON 94637 was not a major contributor of composition variation in the grain and that the observed statistical differences were therefore not biologically meaningful. Bayer therefore concluded that the results of the nutrient composition assessment demonstrate that grain derived from MON 94637 soybean is compositionally comparable to that of non-GE control soybean and other soybean varieties with a history of safe use in food.

---

[3] 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. Series on the Safety of Novel Foods and Feeds No. 25. Paris, France, Organisation for Economic Co-operation and Development, ENV/JM/MONO (2012)24.

[4] AFSI (2022) Crop Composition Database, Version 8.0. Agriculture & Food Systems Institute, https://www.cropcomposition.org/ (Accessed February 22, 2022).

## Conclusion

Based on the information provided by Bayer and other information available to HFP, we have no further questions at this time about the safety, nutrition, and regulatory compliance of human food from MON 94637 soybean. We consider the consultation with Bayer on MON 94637 soybean to be complete.

Charles Kanobe -S

Digitally signed by Charles Kanobe -S
Date: 2024.11.26 14:08:32 -05'00'

Charles Kanobe, Ph.D.