



Biotechnology Notification File No. 000186 CVM Note to the File

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To: Administrative Record, BNF No. 000186

Subject: Event MON 95275 Corn

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Purpose

This document summarizes the Food and Drug Administration (FDA) Center for Veterinary Medicine's (CVM, we) evaluation of biotechnology notification file (BNF) number 000186. Bayer CropScience LP (Bayer) submitted a safety and nutritional assessment for a genetically engineered (GE) corn, transformation event MON 95275 (hereafter referred to as MON 95275 corn), and additional information afterwards. CVM evaluated the information in Bayer's submissions to ensure that regulatory and safety issues regarding animal food derived from MON 95275 corn have been resolved prior to commercial distribution. FDA's Center for Food Safety and Applied Nutrition summarizes its evaluation of MON 95275 corn in human food in a separate document.

In CVM's evaluation, we considered all of the information provided by Bayer 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 effects of the modifications in MON 95275 corn are to confer resistance to targeted coleopteran pests, including western corn rootworm (*Diabrotica virgifera virgifera*) and northern corn rootworm (*Diabrotica barberi*). To confer insect resistance, Bayer introduced: the *mpp75Aa1.1* gene from *Brevibacillus laterosporus* that encodes for the Mpp75Aa1.1 protein; the *vpb4Da2* gene from *Bacillus thuringiensis* that encodes for Vpb4Da2 protein; and the *DvSnf7.1* double-stranded ribonucleic acid

(dsRNA) transcripts, derived from the *DvSnf7* gene of the western corn rootworm, that trigger an RNA-mediated silencing mechanism.¹

Regulatory Considerations

The purpose of this evaluation is to determine whether use of the new plant variety in animal food raises safety or regulatory issues under the Federal Food, Drug and Cosmetic Act (FD&C Act).

The Environmental Protection Agency (EPA) defines a plant-incorporated protectant (PIP) 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” (40 CFR 174.3). EPA regulates PIPs under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the FD&C Act. Under EPA regulations, the *mpp75Aa1.1* expression cassette, the *vpb4Da2* expression cassette, and the *dvsnf7.1* dsRNA expression cassette in MON 95275 corn and the resulting expression products are considered pesticidal substances. Therefore, the safety assessment of these products falls under the regulatory purview of EPA.

Inheritance and Stability

Bayer characterized the insertion event and genomic stability of the insert in the MON 95275 corn genome using bioinformatics techniques based on data obtained from whole genome sequencing (WGS), junction sequence analysis (JSA), and directed sequencing. To confirm genomic stability, Bayer performed WGS on multiple breeding generations of MON 95275 corn. Bayer detected two identical junction sequences² in each of the generations tested, indicating a single site of insertion, and, as anticipated, no junction sequences were observed in the control lines.

In addition, Bayer assessed inheritance of the inserted transfer DNA in MON 95275 corn in both inbred and outbred lines using event-specific polymerase chain reaction. The results of Chi-square analysis of the segregation data from three generations show that the segregation pattern of the insert is consistent with Mendelian principles of inheritance for a single locus. Bayer concludes that the insert in MON 95275 corn was integrated at one locus and is stably transmitted across multiple generations.

¹ Bayer states that the *5-enolpyruvylshikimate-3-phosphate synthase* (*cp4 epsps*) gene from *Agrobacterium tumefaciens* strain CP4, which encodes a CP4 EPSPS protein that confers tolerance to the herbicide glyphosate, was used as a selectable marker and was subsequently removed during the development of MON 95275 corn.

² Zastrow-Hayes, Gina M et al. “Southern-by-Sequencing: A Robust Screening Approach for Molecular Characterization of Genetically Modified Crops.” *The plant genome* vol. 8,1 (2015): eplantgenome2014.08.0037.

Animal Food Use

Bayer references the Organisation for Economic Co-operation and Development (OECD) consensus document on compositional considerations of maize³ and states that corn (*Zea mays* L.) is a commodity crop grown worldwide for various uses, including human and animal food. Bayer notes that corn has been a staple of human diet for centuries. Corn and its processed fractions have also been used in foods for animals. The production and different methods of processing as well as uses are described in greater detail in the OECD consensus document.

Composition

Scope of Analysis

Bayer analyzed the nutrient composition of MON 95275 corn hybrid and a non-GE corn hybrid variety with a similar genetic background (control) and harvested under similar conditions. Compositional analyses on grain and forage samples were reported for components listed in the OECD corn composition consensus document.

Study Design

Bayer conducted field trials in 2019 at five sites in the United States. A randomized complete block design with four replicate plots at each field site was used. The MON 95275 corn and the conventional control were grown under normal agronomic field conditions for their respective regions. Bayer harvested grain and forage from each replicate within each site for composition analysis. Grain was harvested at physiological maturity and shipped at ambient temperature from the field sites. Forage samples were harvested at R5 growth stage and were shipped on dry ice from the field sites to Bayer. A subsample for compositional analysis was obtained from grain and forage samples from each replicate at each site and stored at not less than -20°C prior to nutrient analyses.

For statistical analysis, Bayer combined composition data for each component from MON 95275 corn and the control across locations using a linear mixed model with site and replicate as random factors. T-test analyses were used to test at the level of $P \leq 0.05$ for differences between MON 95275 corn and control. Differences between MON 95275 corn and control were evaluated based on natural variability defined by values for conventional corn varieties in the International Life Sciences Institute (ILSI) Crop Composition Database (CCDB)⁴ or in the scientific literature. Results were all expressed on a dry matter basis prior to statistical analyses except for fatty acids, which were expressed on a percent of total fatty acids basis. Moisture of forage and grain were not statistically analyzed.

Results of Analyses

For forage, Bayer reports values for proximates (crude protein, crude fat, carbohydrates by calculation, and ash), fiber (acid detergent fiber (ADF) and neutral detergent fiber

³ Organisation for Economic Co-operation and Development. 2002. Consensus document on compositional considerations for new varieties of maize (*Zea mays*): Key food and feed nutrients, anti-nutrients, and secondary plant metabolites. OECD ENV/JM/MONO 25. OECD, Paris, France.

⁴ The ILSI Crop Composition Database has become the Agriculture and Food Systems Institute Crop Composition Database and is available at www.cropcomposition.org.

(NDF)), calcium, and phosphorus. Bayer found no statistically significant differences between the control and MON 95275 corn in these components and, therefore, Bayer concludes there are no biologically meaningful differences from an animal food safety perspective.

For grain, Bayer chemically analyzed proximates, fiber (ADF, NDF, and total dietary fiber), 18 amino acids, 22 fatty acids, 9 minerals, 7 vitamins, 2 anti-nutrients and 3 secondary metabolites. Bayer noted that 13 of the fatty acids, sodium, and furfural were not statistically analyzed because more than 50% of the observations fell below the lower limits of quantitation (LOQ). Bayer reports statistically significant differences between the control and MON 95275 corn in the levels of 7 components (palmitic acid, stearic acid, oleic acid, linoleic acid, arachidic acid, calcium and vitamin B₆). For these components, the mean difference between MON 95275 corn and the control was less than the range of values for the control and within the mean ranges of the natural varieties observed in the literature and/or the ILSI-CCDB. Bayer concludes that the differences in these components between MON 95275 corn and the control are not biologically meaningful from an animal food safety perspective.

Summary of Compositional Analyses

Bayer states based on the results from the compositional analyses that forage and grain obtained from MON 95275 corn are not biologically different from those of the control and reference varieties. Bayer concludes that these results support the conclusion that forage and grain obtained from MON 95275 corn are compositionally comparable to the control in the levels of key nutrients, anti-nutrients, and secondary metabolites.

Conclusion

CVM evaluated Bayer's submissions to determine whether MON 95275 corn raises any safety or regulatory issues with respect to its use in animal food. Based on the information provided by Bayer 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.

Bayer concludes that MON 95275 corn 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 corn varieties now grown, marketed, and consumed. At this time, based on Bayer's data and information, CVM considers Bayer's consultation on MON 95275 corn for use in animal food to be complete.

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