
Biotechnology Consultation – Note to the File Biotechnology Notification File No. 000160

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To: Administrative Record, BNF No. 000160

Subject: MON 88702 Insect Resistant Cotton

Keywords: cotton; *Gossypium hirsutum* L.; insect resistant; Cry51Aa2.834_16; mCry51Aa2; *Bacillus thuringiensis* (*Bt*); MON 88702; Monsanto; OECD Unique Identifier MON-88702-4

Purpose

This document summarizes the Food and Drug Administration's (FDA's, our) evaluation of biotechnology notification file (BNF) No. 000160. Monsanto Company (Monsanto)¹ submitted a safety and nutritional assessment of genetically engineered insect resistant cotton transformation event MON 88702 (MON 88702 cotton), which we received on March 29, 2017. We received additional information from Monsanto on November 10, 2017. We evaluated the information in Monsanto's submission to ensure that regulatory and safety issues regarding human or animal food derived from MON 88702 cotton have been resolved prior to commercial distribution.

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

Intended Effects

Monsanto introduced a modified Cry51Aa2 insecticidal crystal protein, Cry51Aa2.834_16 (mCry51Aa2), derived from *Bacillus thuringiensis* (*Bt*) to protect against feeding damage caused by targeted hemipteran and thysanopteran insect pests.

Regulatory Considerations

The purpose of this evaluation is to determine whether use of the new plant variety in human or 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 in the produce thereof, and the genetic material necessary for production of such a pesticidal substance," including, "any inert

¹ We note that during the course of our evaluation, Monsanto Company was acquired by Bayer, and is now known as Bayer U.S. – Crop Science.

ingredient contained in the plant, or produce thereof” (40 CFR 174.3). EPA regulates PIPs under the Federal Insecticide, Fungicide, and Rodenticide Act and the FD&C Act. Under EPA’s regulations, the *mCry51Aa2* gene in MON 88702 cotton and the resulting expression product are considered pesticidal substances.²

Inheritance and Stability

Monsanto characterized the insertion³ in MON 88702 cotton and genomic stability of the insert using bioinformatics techniques based on data obtained from whole genome sequencing (WGS), junction sequence analysis (JSA), and directed sequencing. Monsanto used the KAPA Hyper Prep Kit (Kapa Biosystems) to generate data with an average individual sequence read length of approximately 125 base pairs. Monsanto estimated that it collected sufficient data to cover the cotton genome at least 80x fold. Monsanto identified sequence data spanning insert junctions and used the number of unique junction sequences to infer the number of insertion sites. Monsanto confirmed the integrity of the nucleotide sequence for the insert through directed sequencing. Monsanto analyzed the insertion at the 5’ and 3’ genomic junctions using bioinformatics analyses. Monsanto concludes that it is unlikely the insertion would result in safety issues involving allergenic or toxic effects.

Monsanto performed WGS and JSA on a total of five breeding generations to confirm the genomic stability and Mendelian inheritance pattern of the inserted DNA. Monsanto detected identical junction sequences in each of the generations tested. Monsanto concludes that the insert was integrated at a single, chromosomal locus and is stably transmitted over multiple generations.

Human and Animal Food Uses

Cottonseed is a by-product of textile fiber production; it is used in human and animal food and a range of industrial products. Food uses of cottonseed include cottonseed oil and cotton linters. Cottonseed oil is highly refined to remove naturally occurring toxicants, gossypol and cyclopropenoid fatty acids (CPFAs). Cottonseed oil is primarily consumed as a salad or cooking oil. Cotton linters are short fibers that remain on cotton seeds after ginning. They are removed from the seeds and processed into pure cellulose, which is used, for example, in casings for bologna, sausages, and frankfurters and in other products such as ice cream or salad dressings.

Whole cottonseed, cottonseed meal, crude cottonseed oil, hulls, and cotton gin trash are used in animal food for cattle, sheep, goats, horses, poultry, swine, fish, and shrimp. Cottonseed meal is obtained from the flakes or cake after oil removal; it is used as a protein supplement in animal food. Cottonseed hulls are used as a source of fiber in animal food.

Composition

Scope of Analysis

Monsanto analyzed the composition of acid de-linted cottonseed obtained from MON 88702 and the parental control, DP393 (control). Monsanto selected components for analysis from those recommended in the OECD consensus document for cotton composition.⁴

² Tolerance exemptions for nucleic acids in plant incorporated protectants and for the Cry51Aa2.834_16 protein in cotton are listed in 40 CFR174.507 and 40 CFR 174.539, respectively.

³ The *aadA* gene, present in a second expression cassette, encodes for the aminoglycoside-modifying enzyme 3”(9)-O-nucleotidyltransferase that was used as a selectable marker for transformation. The *aadA* gene was removed through traditional breeding, segregation, selection, and screening.

⁴ OECD. 2009. Consensus document on the compositional considerations for new varieties of cotton (*Gossypium hirsutum* and *G. barbadense*): Key food and feed nutrients and anti-nutrients. ENV/JM/MONO(2004)16. Organisation for Economic Co-operation and Development, Paris, France.

Study Design - Compositional Analyses

Monsanto states that cottonseed was obtained from plants grown at five field sites across the U.S. in a randomized complete block design with four replicates at each site. MON 87702 and control were grown under agronomic field conditions typical for the different growing regions.

Using a mixed model analysis of variance method, Monsanto statistically assessed values from proximates (crude protein, total fat, ash, and carbohydrate by calculation), fiber (acid detergent fiber and neutral detergent fiber), five anti-nutrients (total gossypol, free gossypol, malvalic acid, sterculic acid, and dihydrosterculic acid), 18 amino acids, and linoleic acid. Differences observed were considered statistically significant based on an alpha level of 0.05. When a statistically significant difference was observed for a component in cottonseed obtained from MON 88702 and the control, Monsanto assessed whether the difference was biologically meaningful regarding human and animal food safety. Monsanto compared the mean levels of the components obtained from MON 88702 cotton with those from the control, within the context of levels reported in the literature and the International Life Sciences Institute Crop Composition Database (ILSI-CCDB).

Results and Summary of Compositional Analyses

Monsanto found no statistically significant differences for 29 of 30 components including 3 proximates, 5 anti-nutrients, 18 amino acids, and linoleic acid; there was a small, but statistically significant difference in crude protein. The mean value for crude protein in MON 88702 cotton fell within the ranges of values observed in the literature and the ILSI-CCDB. Monsanto considers that the statistically significant difference in crude protein between MON 87702 cotton and the control is not biologically meaningful from a human or animal food safety perspective. Therefore, Monsanto concludes that MON 88702 cotton is compositionally comparable to conventional cotton.

Conclusion

FDA evaluated Monsanto's submission to determine whether MON 88702 cotton raises any safety or regulatory issues with respect to its uses in human or animal food. Based on the information provided by the company and other information available to the agency, FDA did not identify any safety or regulatory issues under the FD&C Act that would require further evaluation at this time.

Monsanto has concluded that its insect-resistant cotton variety MON 88702 and the human and animal foods derived from it are as safe as conventional cotton varieties and are not materially different in composition or any other relevant parameter from other cotton varieties now grown, marketed, and consumed. At this time, based on Monsanto's data and information, the agency considers Monsanto's consultation on MON 88702 cotton to be complete.

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