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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 174

[EPA-HQ-OPP-2016-0279; FRL-9957-23]

Bacillus Thuringiensis (mCry51Aa2) Protein in or on Cotton; Temporary Exemption from the Requirement of a Tolerance

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: This regulation establishes a temporary exemption from the requirement of a tolerance for residues of the *Bacillus thuringiensis* mCry51Aa2 protein in or on the food and feed commodities of cotton; cotton undelinted seed; cotton, gin byproducts; cotton, forage; cotton, hay; cotton, hulls; cotton, meal; and cotton, refined oil, when used as a plant-incorporated protectant (PIP) in accordance with the terms of Experimental Use Permit (EUP) No. 524-108. Monsanto Company submitted a petition to EPA under the Federal Food, Drug, and Cosmetic Act (FFDCA), requesting the temporary tolerance exemption. This regulation eliminates the need to establish a maximum permissible level for residues of mCry51Aa2 protein. The temporary tolerance exemption expires on February 28, 2019.

DATES: This regulation is effective [*insert date of publication in the Federal Register*]. Objections and requests for hearings must be received on or before [*insert date 60 days after date of publication in the Federal Register*], and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Unit I.C. of the **SUPPLEMENTARY INFORMATION**).

ADDRESSES: The docket for this action, identified by docket identification (ID) number EPA-HQ-OPP-2016-0279, is available at <http://www.regulations.gov> or at the Office of Pesticide Programs Regulatory Public Docket (OPP Docket) in the Environmental Protection Agency Docket Center (EPA/DC), West William Jefferson Clinton Bldg., Rm. 3334, 1301 Constitution Ave., NW., Washington, DC 20460-0001. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the OPP Docket is (703) 305-5805. Please review the visitor instructions and additional information about the docket available at <http://www.epa.gov/dockets>.

FOR FURTHER INFORMATION CONTACT: Robert McNally, Biopesticides and Pollution Prevention Division (7511P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; main telephone number: (703) 305-7090; email address: BPPDFRNotices@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. The following list of North American Industrial Classification System (NAICS) codes is not intended to be exhaustive, but rather provides a guide to help readers determine whether this document applies to them. Potentially affected entities may include:

- Crop production (NAICS code 111).

- Animal production (NAICS code 112).
- Food manufacturing (NAICS code 311).
- Pesticide manufacturing (NAICS code 32532).

B. How Can I Get Electronic Access to Other Related Information?

You may access a frequently updated electronic version of 40 CFR part 174 through the Government Printing Office's e-CFR site at http://www.ecfr.gov/cgi-bin/text-idx?&c=ecfr&tpl=/ecfrbrowse/Title40/40tab_02.tpl.

C. How Can I File an Objection or Hearing Request?

Under FFDCA section 408(g), 21 U.S.C. 346a, any person may file an objection to any aspect of this regulation and may also request a hearing on those objections. You must file your objection or request a hearing on this regulation in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA-HQ-OPP-2016-0279 in the subject line on the first page of your submission. All objections and requests for a hearing must be in writing, and must be received by the Hearing Clerk on or before *[insert date 60 days after date of publication in the **Federal Register**]*. Addresses for mail and hand delivery of objections and hearing requests are provided in 40 CFR 178.25(b).

In addition to filing an objection or hearing request with the Hearing Clerk as described in 40 CFR part 178, please submit a copy of the filing (excluding any Confidential Business Information (CBI)) for inclusion in the public docket. Information not marked confidential pursuant to 40 CFR part 2 may be disclosed publicly by EPA without prior notice. Submit the non-CBI copy of your objection or hearing request,

identified by docket ID number EPA-HQ-OPP-2016-0279, by one of the following methods:

- *Federal eRulemaking Portal*: <http://www.regulations.gov>. Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be CBI or other information whose disclosure is restricted by statute.

- *Mail*: OPP Docket, Environmental Protection Agency Docket Center (EPA/DC), (28221T), 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001.

- *Hand Delivery*: To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at <http://www.epa.gov/dockets/contacts.html>.

Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at <http://www.epa.gov/dockets>.

II. Background and Statutory Findings

In the **Federal Register** of June 22, 2016 (81 FR 40594) (FRL-9947-32), EPA issued a document pursuant to FFDCA section 408(d)(3), 21 U.S.C. 346a(d)(3), announcing the filing of a pesticide tolerance petition (PP 6G8453) by Monsanto Company, 800 North Lindbergh Blvd., St. Louis, MO 63167. The petition requested that 40 CFR part 174 be amended by establishing a temporary exemption from the requirement of a tolerance for residues of the plant-incorporated protein (PIP) *Bacillus thuringiensis* mCry51Aa2.834_16 (mCry51Aa2) protein in or on cotton. That document referenced a summary of the petition prepared by the petitioner Monsanto Company, which is available in the docket, <http://www.regulations.gov>. One comment was received on the notice of filing. EPA's response to this comment is discussed in Unit VII.C.

Section 408(c)(2)(A)(i) of FFDCA allows EPA to establish an exemption from the requirement for a tolerance (the legal limit for a pesticide chemical residue in or on a food) only if EPA determines that the exemption is “safe.” Section 408(c)(2)(A)(ii) of FFDCA defines “safe” to mean that “there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.” This includes exposure through drinking water and in residential settings, but does not include occupational exposure. Pursuant to FFDCA section 408(c)(2)(B), in establishing or maintaining in effect an exemption from the requirement of a tolerance, EPA must take into account the factors set forth in FFDCA section 408(b)(2)(C), which require EPA to give special consideration to exposure of infants and children to the pesticide chemical residue in establishing a tolerance and to “ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue....” Additionally, FFDCA section 408(b)(2)(D) requires that the Agency consider “available information concerning the cumulative effects of a particular pesticide's residues” and “other substances that have a common mechanism of toxicity.”

EPA performs a number of analyses to determine the risks from aggregate exposure to pesticide residues. First, EPA determines the toxicity of pesticides. Second, EPA examines exposure to the pesticide through food, drinking water, and through other exposures that occur as a result of pesticide use in residential settings.

III. Toxicological Profile

Consistent with FFDCA section 408(b)(2)(D), EPA has reviewed the available scientific data and other relevant information in support of this action and considered its

validity, completeness and reliability, and the relationship of this information to human risk. EPA has also considered available information concerning the variability of the sensitivities of major identifiable subgroups of consumers, including infants and children.

Bacillus thuringiensis (Bt) Cry (or crystalline) proteins are naturally produced. These insecticidal proteins are protoxins, which must be activated by alkaline conditions in the insect gut, so they are not toxic until ingested by an insect. When activated, specific binding sites found only in susceptible host insects are involved in binding *Bt* protein toxins, followed by pore formation into the insect hemolymph, leakage and, in general, decreased vitality of the insect including reduced feeding, eventually causing mortality. Even among insects, specific *Bt* proteins are highly specific and so selection of specific proteins to target pests is possible often with little or no nontarget effects to humans or even to other insects.

Bt proteins are also ubiquitous in soil and water and are found on food products which may be consumed with little processing. No adverse effects are expected or have been reported from exposure to *Bt* Cry proteins. Further, the use of *Bt* insecticidal proteins in bacterial and plant-incorporated formulations over time has been widely shown to be safe and nontoxic except to a limited range of target pests.

Minor alterations to the native (or naturally produced) Cry51Aa2 protein were made to make the protein Cry51Aa2.834_16 (hereafter referred to as modified Cry51Aa2 or mCry51Aa2) more active and specific to the target insect pests Lygus bugs and Thrips, when the protein is expressed in cotton plant tissues.

Molecular analysis of mCry51Aa2 showed that it has a protein sequence that is 98% similar to Cry51Aa1 protoxin and 96% similar to the native Cry51Aa2 protoxin.

Other sequence alignments, ranging from 27 to 96%, were to *Bacillus* proteins.

Comparisons using the Basic Local Alignment Search Tool – protein query (BLASTp) database found 16 significant alignments, and all except the uncharacterized *Jatropha curcas* protein are from genus *Bacillus*. However, only three have identity >35% similarity and these are related insecticidal *Bacillus thuringiensis* Cry proteins/protoxins. Comparison of mCry51Aa2 to the native Cry51Aa2 using the FASTA database shows three amino acids were deleted, and there are seven substitutions to the original 309 amino acids, resulting in a 306 amino acid protoxin. There were no sequences with any significant similarity (>35%) to known toxins other than the insecticidal protoxins from *Bacillus thuringiensis*.

An acute oral toxicity test conducted with mice at the highest practicable dose of dose of 1332 mg of mCry51Aa2/ Kg body weight was conducted in mice and showed no clinical signs of toxicity, no abnormalities on necropsy 14 days after treatment, and no statistically significant weight fluctuation. The No observed adverse effect level (NOAEL) was determined to be > 1332 milligram (mg) of mCry51Aa2 per kilogram (kg) bodyweight.

Rapid digestibility by pepsin was demonstrated (93.7% reduction within two minutes, and no detects at 60 minutes). Based on this assay it is likely that mCry51Aa2 would be completely digested in the human stomach.

A thorough analysis of mCry51Aa2 shows it is not related to any other known allergens. Molecular analysis showed there were no significant full-length allergen sequence matches, and none showed significant similarity using a sliding 80 amino acid search or an exact 8 amino acid match.

Based on the results of these studies, no toxicity or other adverse effects from dietary exposure to mCry51Aa2 are expected.

IV. Aggregate Exposures

In examining aggregate exposure, FFDCa section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

The Agency considered available information on the aggregate exposure levels of consumers (and major identifiable subgroups of consumers) to the pesticide residue. These considerations include dietary exposure under the tolerance exemption in effect for the *Bt* mCry51Aa2 protein residue, and exposure from non-occupational sources. Oral exposure may occur at very low levels from ingestion of food and feed commodities of cotton. With respect to drinking water, since the PIP is integrated into the plant genome and based upon EPA's human health and environmental assessments for *Bt* mCry51Aa2 protein (Refs. 1 and 2), the Agency expects residues in drinking water to be extremely low or non-existent.

Exposure via the skin or inhalation is not likely since the plant-incorporated protectant is contained within plant cells, which essentially eliminates these exposure routes or reduces exposure by these routes to negligible. Exposure to infants and children via residential or lawn use is also not expected because the use is limited to agricultural production of cotton with the *Bt* mCry51Aa2 protein PIP.

V. Cumulative Effects from Substances with a Common Mechanism of Toxicity

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider “available information” concerning the cumulative effects of a particular pesticide’s residues and “other substances that have a common mechanism of toxicity.”

EPA has not found mCry51Aa2 protein to share a common mechanism of toxicity with any other substances, and mCry51Aa2 protein does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has assumed that mCry51Aa2 protein does not have a common mechanism of toxicity with other substances. For information regarding EPA’s efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see EPA’s website at <http://www.epa.gov/pesticides/cumulative>.

VI. Determination of Safety for U.S. Population, Infants and Children

FFDCA section 408(b)(2)(C) provides that, in considering the establishment of a tolerance or tolerance exemption for a pesticide chemical residue, EPA shall assess the available information about consumption patterns among infants and children, special susceptibility of infants and children to pesticide chemical residues, and the cumulative effects on infants and children of the residues and other substances with a common mechanism of toxicity. In addition, FFDCA section 408 (b)(2)(C) provides that EPA shall apply an additional tenfold (10X) margin of exposure (safety) for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the database on toxicity and exposure unless EPA determines that a different margin of exposure (safety) will be safe for infants and children. This additional

margin of exposure (safety) is commonly referred to as the Food Quality Protection Act Safety Factor (FQPA SF). In applying this provision, EPA either retains the default value of 10X or uses a different additional safety factor when reliable data available to EPA support the choice of a different factor.

Based on the information discussed in Unit III., EPA concludes that there are no threshold effects of concern to infants, children, or adults from exposure to the *Bt* mCry51Aa2 protein. As a result, EPA concludes that no additional margin of exposure (safety) is necessary to protect infants and children and that not adding any additional margin of exposure (safety) will be safe for infants and children.

Therefore, based on the discussion in Units III. and IV. and the supporting documentation, EPA concludes that there is a reasonable certainty that no harm will result to the U.S. population, including infants and children, from aggregate exposure to the residues of the *Bt* mCry51Aa2 protein in cotton products, when it is used as a plant-incorporated protectant. Such exposure includes all anticipated dietary exposures and all other exposures for which there is reliable information.

VII. Other Considerations

A. Analytical Enforcement Methodology

A standard operating procedure for an enzyme-linked Immunosorbent assay (ELISA) for the detection and quantification of the *Bt* mCry51Aa2 protein in cotton tissue has been submitted.

B. International Residue Limits

In making its tolerance decisions, EPA seeks to harmonize U.S. tolerances with international standards whenever possible, consistent with U.S. food safety standards and

agricultural practices. EPA considers the international maximum residue limits (MRLs) established by the Codex Alimentarius Commission (Codex), as required by FFDC section 408(b)(4). The Codex Alimentarius is a joint United Nations Food and Agriculture Organization/World Health Organization food standards program, and it is recognized as an international food safety standards-setting organization in trade agreements to which the United States is a party. EPA may establish a tolerance that is different from a Codex MRL; however, FFDC section 408(b)(4) requires that EPA explain the reasons for departing from the Codex level.

The Codex has not established a MRL for the *Bt* protein mCry51Aa2 protein.

C. Response to Comments

In response to the Notice of Filing (81FR40594), one comment was received and posted August 05, 2016. It urged the Agency deny the request for “*Bt* Cry51Aa2” because “the release of more protein on earth is harmful because our nature exists with a certain set of standards.” The commenter did not provide any more information on the set of standards governing our nature. In response to this comment, the Agency notes that protein is an important component of the diet of humans and animals and that Monsanto Company has submitted information to address the potential for the mCry51Aa protein to be similar to a known allergen or toxin utilizing amino acid similarity analysis. There is no indication from the information provided that the mCry51Aa protein would behave differently from any other dietary protein.

One additional comment about human health effects was received not in response to the Notice of Filing, but in response to the Notice of Receipt for this Experimental Use Permit (81FR48793; see docket EPA-HQ-OPP-2016-0282). Because it raised a concern

about human health effects, the EPA is responding to it in this document. The comment stated that that ‘...numerous studies show toxicity of Bt products including GM Bt crops to other non-target including... rats as well as allergenic and respiratory problems in humans...’ While not all of the numerical citations were provided, it was possible to retrieve several. Some articles (“Ban GMOs Now” and “New GMO Studies Demonstrate ‘Substantial Non-Equivalence’) were not from peer-reviewed journals and are of questionable validity for the issue of mCry51Aa safety. There was a reference to an article about the presence of Bt toxins in the blood of non-pregnant and pregnant females as well as in fetal cord blood. This article by Aris & Leblanc (Repro Tox. 31:528-533, 2011) has some important design limitations which question the implications made in the paper about blood levels of Cry1Ab protein. Most importantly, there were no identified effects in the population sampled that indicates any health concerns related to the presence of the Cry1Ab protein in blood.

Overall there is no substantive information in either of these comments to inform the risk assessment for mCry51Aa2.

VIII. Conclusions

The Agency concludes that there is a reasonable certainty that no harm will result to the U.S. population, including infants and children, from aggregate exposure to residues of mCry51Aa2 protein in or on cotton. This includes all anticipated dietary exposures and all other exposures for which there is reliable information. The Agency has arrived at this conclusion because, as discussed previously no toxicity to mammals has been observed, nor is there any indication of allergenicity potential for the plant-incorporated protectant, and there is a long history of human exposure to *Bacillus*

thuringiensis bacteria and toxins through naturally occurring residues and residues from use as a pesticide in agricultural and residential settings and in other plant incorporated protectants. Therefore, a temporary exemption is established for residues of the PIP *Bacillus thuringiensis* mCry51Aa2 protein on the food and feed commodities derived from cotton containing the PIP.

IX. References

1. U.S. EPA. 2016a. MON 88702 Cotton Expressing *B. thuringiensis* mcry51Aa2 Protein Stacked with the Vip3Aa19, Cry2Ab2 and Cry1Ac Proteins Memorandum from J. Gagliardi, Ph.D. through J. Kough, Ph.D. to A. Sibold, dated September 12, 2016.

2. U.S. EPA. 2016b. Environmental Risk Assessment for a FIFRA Section 5 Experimental Use Permit for MON 88702 Alone and in Combination with Other Registered Plant Incorporated Protectants in Cotton. Memorandum from S. Borges, Senior Scientist. to A. Sibold, Regulatory Action Leader., dated October 19, 2016.

3. U.S. EPA. 2016c. Review of Public Comments on Cry51Aa Notice of Filing Experimental Use Permit and Associated Temporary Tolerance (6G8453). November 2, 2016.

X. Statutory and Executive Order Reviews

This action establishes a tolerance under FFDCA section 408(d) in response to a petition submitted to the Agency. The Office of Management and Budget (OMB) has exempted these types of actions from review under Executive Order 12866, entitled “Regulatory Planning and Review” (58 FR 51735, October 4, 1993). Because this action has been exempted from review under Executive Order 12866, this action is not subject to Executive Order 13211, entitled “Actions Concerning Regulations That Significantly

Affect Energy Supply, Distribution, or Use” (66 FR 28355, May 22, 2001) or Executive Order 13045, entitled “Protection of Children from Environmental Health Risks and Safety Risks” (62 FR 19885, April 23, 1997). This action does not contain any information collections subject to OMB approval under the Paperwork Reduction Act (PRA) (44 U.S.C. 3501 *et seq.*), nor does it require any special considerations under Executive Order 12898, entitled “Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations” (59 FR 7629, February 16, 1994).

Since tolerances and exemptions that are established on the basis of a petition under FFDCA section 408(d), such as the tolerance in this final rule, do not require the issuance of a proposed rule, the requirements of the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 *et seq.*), do not apply.

This action directly regulates growers, food processors, food handlers, and food retailers, not States or tribes, nor does this action alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of FFDCA section 408(n)(4). As such, the Agency has determined that this action will not have a substantial direct effect on States or tribal governments, on the relationship between the national government and the States or tribal governments, or on the distribution of power and responsibilities among the various levels of government or between the Federal Government and Indian tribes. Thus, the Agency has determined that Executive Order 13132, entitled “Federalism” (64 FR 43255, August 10, 1999) and Executive Order 13175, entitled “Consultation and Coordination with Indian Tribal Governments” (65 FR 67249, November 9, 2000) do not apply to this action. In addition, this action does not impose any enforceable duty or contain any unfunded mandate as

described under Title II of the Unfunded Mandates Reform Act (UMRA) (2 U.S.C. 1501 *et seq.*).

This action does not involve any technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act (NTTAA) (15 U.S.C. 272 note).

XI. Congressional Review Act

Pursuant to the Congressional Review Act (5 U.S.C. 801 *et seq.*), EPA will submit a report containing this rule and other required information to the U.S. Senate, the U.S. House of Representatives, and the Comptroller General of the United States prior to publication of the rule in the **Federal Register**. This action is not a “major rule” as defined by 5 U.S.C. 804(2).

List of Subjects in 40 CFR Part 174

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: January 10, 2017,

Robert McNally,

Division Director, Biopesticides and Pollution Prevention Division, Office of Pesticide Programs.

Therefore, 40 CFR chapter I is amended as follows:

PART 174--AMENDED

1. The authority citation for part 174 continues to read as follows:

Authority: 21 U.S.C. 321(q), 346a and 371.

2. Add § 174.536 to subpart W to read as follows:

§174.536 *Bacillus thuringiensis* mCry51Aa2 protein in cotton; temporary exemption from the requirement of a tolerance.

Residues of the protein mCry51Aa2 in or on the food and feed commodities of cotton: cotton, undelinted seed; cotton, gin byproducts; cotton, forage; cotton, hay; cotton, hulls; cotton, meal; and cotton, refined oil are temporarily exempt from the requirement of a tolerance when used as a plant-incorporated protectant in cotton plants in accordance with the terms of Experimental Use Permit No. 524-EUP-108. This temporary exemption from the requirement of a tolerance expires on February 28, 2019.

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