



ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA-HQ-OPP-2021-0269; FRL-10944-01-OCSP]

Ledprona Double-stranded RNA; Exemption from the Requirement of a Tolerance

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: This regulation establishes an exemption from the requirement of a tolerance for residues of Ledprona double-stranded (ds) RNA in or on potato when used as a foliar-applied insecticide for the selective control of Colorado potato beetle and in accordance with label directions and good agricultural practices. GreenLight Biosciences, Inc. submitted a petition to EPA under the Federal Food, Drug, and Cosmetic Act (FFDCA), requesting an exemption from the requirement of a tolerance. This regulation eliminates the need to establish a maximum permissible level for residues of Ledprona dsRNA under FFDCA when used in accordance with this exemption.

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-2021-0269, is available online at <https://www.regulations.gov>. Please review the visitor instructions and additional information about the docket available at <https://www.epa.gov/dockets>.

FOR FURTHER INFORMATION CONTACT: Madison Le, Biopesticides and Pollution Prevention Division (7511M), 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 180 through the Government Printing Office's e-CFR site at <https://www.ecfr.gov/current/title-40>. To access the OCSPP test guidelines referenced in this document electronically, please go to <https://www.epa.gov/ocspp> and select “Test Methods and Guidelines.”

C. How can I file an objection or hearing request?

Under FFDCA section 408(g), 21 U.S.C. 346a(g), 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-2021-0269 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-2021-0269, by one of the following methods:

- *Federal eRulemaking Portal:* <https://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 <https://www.epa.gov/dockets/contacts.html>.

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

II. Background and Statutory Findings

In the **Federal Register** of June 28, 2021 (86 FR 33922) (FRL-10025-08), 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 1F8900) by GreenLight Biosciences, Inc., 200 Boston Ave., Suite 1000, Medford, MA 02155. The petition requested that 40 CFR part 180 be amended by establishing an exemption from the requirement of a tolerance for residues of Ledprona dsRNA in or on all agricultural commodities and food products. That document referenced a summary of the petition prepared by the petitioner GreenLight Biosciences, Inc., which is available in the

docket, <https://www.regulations.gov>. There were no comments received in response to the notice of filing.

Based upon review of the data supporting the petition and in accordance with its authority under FFDCFA section 408(d)(4)(A)(i), EPA is establishing a tolerance exemption for residues of Ledprona dsRNA in or on potato only, rather than all agricultural commodities and food products as requested. The reasons for this change are explained in Unit III.C.

In addition, EPA previously established a temporary tolerance exemption for residues of Ledprona dsRNA in or on potato (40 CFR 180.1403; 88 FR 28427) in conjunction with Experimental Use Permit (EUP) No. 94614-EUP-1 issued to GreenLight BioSciences, Inc. in May 2023. The temporary tolerance exemption expires on April 30, 2025. Because this action establishes a permanent tolerance exemption for residues of Ledprona dsRNA in or on potato, EPA is removing the temporary tolerance exemption as no longer necessary.

III. Final Rule

A. EPA's Safety Determination

Section 408(c)(2)(A)(i) of FFDCFA 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 FFDCFA 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 it does not include occupational exposure. Pursuant to FFDCFA 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 FFDCFA section 408(b)(2)(C) and (D). FFDCFA section 408(b)(2)(C) requires 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 factors including “available information concerning the cumulative effects of a particular pesticide's residues” and “other substances that have a common mechanism of toxicity.”

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. A full explanation of the data upon which EPA relied and its risk assessment based on those data can be found within the document entitled “Final human health risk assessment, review of product characterization and manufacturing process for the new end-use product, Calantha™, containing 0.8% of the new active ingredient “Ledprona” dsRNA” (Human Health Risk Assessment). This document, as well as other relevant information, is available in the docket for this action at docket ID number EPA-HQ-OPP-2021-0269.

Ledprona (CAS# 2433753-68-3) consists of double-stranded ribonucleic acid (dsRNA) that induces mortality of the Colorado potato beetle (*Leptinotarsa decemlineata*) via a gene silencing mode of action. When dsRNA is applied, it causes the inhibition (or silencing) of the gene product, messenger RNA (mRNA), preventing the translation of the mRNA to proteins. Ledprona dsRNA targets the *Proteasome subunit beta type-5 (PSMB5)* mRNA sequence in the Colorado potato beetle. PSMB5 mRNA encodes a protein that regulates proper folding of other proteins in the Colorado potato beetle. Once Ledprona is ingested by the Colorado potato beetle, over time the lack of PSMB5 mRNA leads to the reduction of the PSMB5 protein and ultimately causes mortality.

Available data and scientific information have demonstrated that, with regard to humans, Ledprona presents no adverse effects of concern and exposure to the active ingredient will be

insignificant. Dietary and drinking water exposure resulting from the proposed use is expected to be minimal due to the following factors: (1) the application rate is low (0.53 oz/acre/calendar year); (2) residues of Ledprona dsRNA on food will be limited, as Ledprona dsRNA is a foliar insecticide and is expected to undergo rapid degradation due to microbes in the environment once applied; (3) mammals possess physiological barriers to dsRNA uptake (i.e., nucleases in saliva and the gastrointestinal tract, acidic conditions in the stomach, and presence of multiple membrane barriers); and (4) Ledprona dsRNA degrades rapidly in simulated gastric and intestinal fluids, including when combined with certain tank mix components (i.e., fungicides and insecticides commonly used on potatoes). This information allows EPA to rely on a well-established history of exposure to RNA molecules via food and supports the conclusion that dietary exposure from the use of the active ingredient will be negligible.

With respect to dietary and drinking water hazards, submitted data demonstrate that Ledprona dsRNA is expected to pose minimal hazard. Ledprona dsRNA was found to have low toxicity via the oral route of exposure (EPA Toxicity Category IV). In addition, a bioinformatic analysis was conducted to evaluate the likelihood of off-target effects of the Ledprona dsRNA in humans *in silico* (i.e., by computer analysis of Ledprona RNA segments). This analysis identified two potential human transcripts as “off targets.” However, further analyses of these transcripts coupled with the specificity of Ledprona dsRNA to its target indicate that Ledprona is not expected to affect these genes *in vivo*, resulting in negligible hazard.

Ledprona is not proposed for residential use and therefore a residential exposure assessment was not conducted. For non-occupational exposure, bystander exposure may occur post-application (i.e., contact with treated foliage or through spray drift of nearby treated areas). Due to the low application rate coupled with spray drift advisories and restrictions on product labels, exposure via contact with treated foliage and spray drift is considered to be negligible. 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.” No risk of cumulative toxicity/effects from Ledprona dsRNA has been identified as no toxicity has been shown for Ledprona dsRNA in the submitted studies. Therefore, EPA has not assumed that Ledprona dsRNA has a common mechanism of toxicity with other substances. Although FFDCA section 408(b)(2)(C) provides for an additional tenfold margin of safety for infants and children in the case of threshold effects, EPA has determined that there are no such effects due to the lack of toxicity of Ledprona dsRNA. As a result, an additional margin of safety for the protection of infants and children is unnecessary.

Based upon the evaluation described above and in the Human Health Risk Assessment, EPA concludes that there is reasonable certainty that no harm will result to the U.S. population, including infants and children, from aggregate exposure to residues of Ledprona dsRNA. This includes all anticipated dietary exposures and all other exposures for which there is reliable information. The Agency has arrived at this conclusion based on the rapid degradation of the active ingredient in environmental and biological conditions, mammalian physiological barriers limiting the uptake of dsRNA, and the lack of effects observed in toxicity testing.

B. Analytical Enforcement Methodology

An analytical method is not required for enforcement purposes since the Agency is establishing an exemption from the requirement of a tolerance without any numerical limitation.

C. Revisions to Petitioned-for Tolerance Exemption

The petitioner requested that EPA establish a permanent tolerance exemption for residues of Ledprona dsRNA in or on all agricultural commodities and food products. EPA previously established a temporary tolerance exemption for residues of Ledprona dsRNA in or on potato in conjunction with EUP No. 94614-EUP-1. The exposure analysis and evaluation of additional data to establish this permanent tolerance exemption is based in part upon the specificity of Ledprona dsRNA to its target organism, the Colorado potato beetle, and the proposed use of Ledprona dsRNA on potatoes. No other use of Ledprona dsRNA on other agricultural

commodities or food products has been proposed. As a result, EPA has not assessed whether use of Ledprona dsRNA on commodities other than potatoes would result in the same dietary exposures described in the current evaluation. Consequently, the permanent tolerance exemption for Ledprona dsRNA residues that EPA is granting in this action varies from what the petitioner sought and is limited to residues of Ledprona dsRNA in or on potato when used as a foliar-applied insecticide for the selective control of Colorado potato beetle and in accordance with label directions and good agricultural practices.

D. Conclusion

Based on the conclusions detailed in Unit III.A. and the Human Health Risk Assessment, 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 residues of Ledprona dsRNA. Therefore, an exemption is established for residues of Ledprona dsRNA in or on potato when used as a foliar-applied insecticide for the selective control of Colorado potato beetle and in accordance with label directions and good agricultural practices. In addition, EPA is replacing the previously established temporary tolerance exemption for Ledprona dsRNA (40 CFR 180.1403) with this permanent tolerance exemption.

IX. Statutory and Executive Order Reviews

Additional information about these statutes and Executive Orders can be found at <https://www.epa.gov/laws-regulations/laws-and-executive-orders#influence>.

A. Executive Orders 12866: Regulatory Planning and Review and 14094: Modernizing Regulatory Review

This action is exempt from review by the Office of Management and Budget (OMB) under Executive Orders 12866, October 4, 1993 (58 FR 51735), as amended by Executive Order 14094 (88 FR 21879, April 11, 2023), because it establishes or modifies a pesticide tolerance or a tolerance exemption under FFDCA section 408, and also applies to tolerance revocations for which extraordinary circumstances do not exist.

B. Paperwork Reduction Act (PRA)

This action does not impose an information collection burden under the PRA, 44 U.S.C. 3501 *et seq.*, because it does not contain any information collection activities.

C. Regulatory Flexibility Act (RFA)

I certify that this action will not have a significant economic impact on a substantial number of small entities under the RFA, 5 U.S.C. 601 *et seq.* In making this determination, EPA concludes that the impact of concern for this rule is any significant adverse economic impact on small entities and that the Agency is certifying that this rule will not have a significant economic impact on a substantial number of small entities because the rule has no net burden on small entities subject to the rule.

D. Unfunded Mandates Reform Act (UMRA)

This action does not contain any unfunded mandate as described in UMRA, 2 U.S.C. 1531-1538, and does not significantly or uniquely affect small governments. The action imposes no enforceable duty on any state, local or tribal governments or the private sector.

E. Executive Order 13132: Federalism

This action does not have federalism implications as specified in Executive Order 13132, August 10, 1999 (64 FR 43255) because it will not have substantial direct effects on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government.

F. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

This action does not have tribal implications as specified in Executive Order 13175, November 9, 2000 (65 FR 67249), because it will not have substantial direct effects on tribal governments, on the relationship between the Federal government and the Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes.

G. Executive Order 13045: Protection of Children from Environmental Health Risks and Safety Risks

This action is not subject to Executive Order 13045 (62 FR 19885, April 23, 1997) because it is not a significant regulatory action under section 3(f)(1) of Executive Order 12866, and because EPA does not believe the environmental health or safety risks addressed by this action present a disproportionate risk to children. However, EPA's *Policy on Children's Health* applies to this action.

This rule finalizes a tolerance action under the FFDCA, which requires 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 ...” (FFDCA 408(b)(2)(C)). Consistent with FFDCA section 408(b)(2)(D), and the factors specified therein, EPA has reviewed the available scientific data and other relevant information in support of this final tolerance action.

H. Executive Order 13211: Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution or Use

This action is not subject to Executive Order 13211, May 22, 2001 (66 FR 28355), because it is not a significant regulatory action under Executive Order 12866.

I. National Technology Transfer Advancement Act (NTTAA)

This action does not involve technical standards under the NTTAA section 12(d), 15 U.S.C. 272.

J. Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

Executive Order 12898 (59 FR 7629, February 16, 1994) directs federal agencies, to the greatest extent practicable and permitted by law, to make environmental justice part of their mission by identifying and addressing, as appropriate, disproportionately high and adverse human health or environmental effects of their programs, policies, and activities on minority populations (people of color and/or indigenous peoples) and low-income populations. EPA has

considered the safety risks for the pesticide subject to this rulemaking and in the context of the tolerance action set out in this rulemaking. EPA believes that the human health and environmental conditions that exist prior to this action do not result in disproportionate and adverse effects on people of color, low-income populations, and/or indigenous peoples. Furthermore, EPA believes that this action is not likely to result in new disproportionate and adverse effects on people of color, low-income populations and/or indigenous peoples.

K. Congressional Review Act (CRA)

This action is subject to the CRA, 5 U.S.C. 801 *et seq.*, and EPA will submit a rule report to each House of the Congress and to the Comptroller General of the United States. This action is not a “major rule” as defined by 5 U.S.C. 804(2).

List of Subjects in 40 CFR Part 180

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

Dated: September 29, 2023.

Edward Messina,

Director, Office of Pesticide Programs.

Therefore, for the reasons stated in the preamble, 40 CFR chapter I is amended as follows:

PART 180 -- TOLERANCES AND EXEMPTIONS FOR PESTICIDE CHEMICAL RESIDUES IN FOOD

1. The authority citation for part 180 continues to read as follows:

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

2. Revise §180.1403 to subpart D to read as follows:

§180.1403 Ledprona double-stranded RNA (CAS# 2433753-68-3); exemption from the requirement of a tolerance.

An exemption from the requirement of a tolerance is established for residues of Ledprona dsRNA in or on potato when used as a foliar-applied insecticide for the selective control of Colorado potato beetle and in accordance with label directions and good agricultural practices.

[FR Doc. 2023-22199 Filed: 10/4/2023 8:45 am; Publication Date: 10/5/2023]