



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

SUBJECT: Revised Section G Experimental Use Program Review for 94614-EUP-R
Assessing Ledprona (CAS# 2433753-68-3) Against Colorado Potato Beetle
on Potatoes

Request Case: 00149125
Action Code Case: 00149127
EPA Reg. Nos.: 94614-EUP-R
MRID: 51838501 (*supersedes*: 51777301)
PC Code: 006550

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Action Requested

Biopesticides and Pollution Prevention Division's (BPPD) Emerging Technologies Efficacy and Insect Resistance Management Team (hereafter, the EPA or the Agency) has reviewed the experimental program (Section G) submitted by GreenLight Biosciences for field testing the new active ingredient, Ledprona (*Leptinotarsa decemlineata*-specific recombinant double-stranded interfering Oligonucleotide GS2), for control of Colorado potato beetle on potato plants.

Summary and Conclusions

GreenLight Biosciences (hereafter GreenLight, or applicant) has applied for an experimental use permit (EUP) EUP under FIFRA Section 5 to test Ledprona (*Leptinotarsa decemlineata*-specific recombinant double-stranded interfering Oligonucleotide GS2) for control of Colorado Potato Beetle (*Leptinotarsa decemlineata*) on potato plants. The EUP application includes an experimental protocol to conduct trials in 10 states on a total of 348 acres and uses a total of 6,360 grams of active ingredient (ai). The duration of the EUP program was proposed for April 2022 through April 2023.

The Agency concludes that the requested use of 6,360 grams of ai to be applied across 348 acres in 10 states is reasonable for GreenLight's experimental objectives intended to establish the efficacy and product performance of Ledprona as applied to potatoes. The requested acreage and amount of product, experimental protocols and methods proposed for testing the efficacy and product performance of Ledprona appear scientifically sound and are justified under Section 5 of FIFRA for generating data to support registration of a pesticide product.

Background

Colorado potato beetle (CPB; *Leptinotarsa decemlineata*) is distributed widely across North America, as well as some areas in Europe and Asia. CPB mainly feeds on Solanum plants, in particular cultivated potato. Other hosts plants include tomato, tobacco, pepper, and eggplant. The potato industry considers CPB one of the most serious defoliating pests. Larvae and adults can cause total yield loss, by skeletonizing a plant, leaving only roots and stem. Use of chemical pesticides has resulted in increased resistance to many classes of pesticides for CPB control. Therefore, an alternative method of control has been investigated. Double stranded RNA (dsRNA) may provide a new mode of action for CPB control.

Ledprona (*Leptinotarsa decemlineata*-specific recombinant double-stranded interfering oligonucleotide GS2) is a new foliarly applied dsRNA-based insecticide. Ledprona at 0.8% is the ai is intended for use to selectively control the CPB in solanaceous crops like potatoes. The ai consists of dsRNA and causes mortality of CPB through a post-transcriptional process called RNA interference (RNAi). Ledprona dsRNA targets, binds to, and interferes with messenger RNA (mRNA) encoding for proteasome subunit beta 5 (dsPSMB5) which in CPB is responsible for catalyzing damaged proteins. The inhibition of dsPSMB5 causes the lethal buildup of protein molecules that cannot be degraded leading to mortality in CPB (Rodrigues et al 2021).

DATA EVALUATION RECORD

Reviewed by: Mick Piombino

Peer Review: Alan Reynolds

Type of Study:	Section G Calculation
MRID:	51838501
Sponsor:	GreenLight Biosciences, Inc.
Report Title:	Experimental Use Permit Application
Author:	Brian Manley, Ph.D.
Study Date:	March 18, 2022
Testing Area:	Proposed for: Idaho, Maine, Michigan, Minnesota, New York, North Dakota, Oregon, Virginia, Wisconsin, Washington
Study ID:	GL-EUP-01
Confidentiality:	No claims of confidentiality
Good Laboratory Practice (GLP):	N/A
Test Material:	Ledprona™ (CAS# 2433753-68-3)
Classification:	Acceptable

Experimental Design

Protocols

GreenLight proposed the following objectives to test during the timeframe of the EUP:

- 1) Evaluate the performance of Ledprona when applied using different application methods (commercial ground sprayers, aerial applications, chemigation) at commercial scale.
- 2) Evaluate the performance of Ledprona compared to industry standard commercial insecticides applied at commercial scale.
- 3) Evaluate the performance of Ledprona when incorporated in various grower IPM programs designed to control CPB.
- 4) Determine how Ledprona affects potato yields when used at a commercial scale.
- 5) Evaluate Ledprona in the presence of several environmental factors (e.g., microbes, nucleases and sunlight/UV), to identify if degradation of Ledprona occurs and/or if performance is affected in commercial field situations and identify ways to mitigate these potential risks.
- 6) Evaluate the effect of Ledprona on different larval stages of CPB by altering the timing of the initial application.

Containment

An exemption from the requirement of a tolerance has been requested with this EUP for residues of Ledprona on potatoes. Therefore, GreenLight does not plan to destroy treated potatoes if the exemption is granted. Treated potatoes will be harvested at some locations and yield data collected, with potato collection conducted by machine or hand-harvesting. Should the tolerance exemption not be granted for the EUP, GreenLight indicates that experimental “potatoes will either be left in the field, buried in the soil or added to a compost pile.” Once the EUP testing is complete, all unused test material will be returned to GreenLight.

Test Location and Acres

The states selected for testing are major potato growing regions including the Pacific Northwest, Upper Midwest, Northeast and parts of the Southeast. The total acres both treated (318 acres) and untreated (9-30 acres) under the EUP equate to a maximum of 348 acres. Thus, the requested acreage for testing product performance and efficacy of Ledprona on potatoes is justifiable based on the location of the testing in major potato growing areas on minimal acreage.

Table 1. Proposed Acres by State (reproduced from Table 8 of MRID 51838501)

State	Number of Growers with large block trials	Treated Acres in large block trials	Number of small plot trials	Total Treated Acres	Untreated Acres
Idaho	0	0	1	1	0.1
Maine	2-3	60	2	62	1-4
Michigan	1	20	1-2	22	1-2
Minnesota	2	40	1-2	42	1-5
New York	2	40	1	41	1-3
North Dakota	1	20	1	21	1-2
Oregon	0-1	20	3	23	1-2
Virginia	0	0	1	1	0.1
Wisconsin	3	60	2	62	1-5
Washington	1-2	40	3	43	1-5
Total		300		318	9-30

* Estimated AI amount assumes a maximum use rate of 4 g ai/acre, and a maximum of 4 applications, plus 25% overage in order to be able to prime sprayers and make appropriate mixtures.

Amount of AI Requested

The applicant has requested 6,360 grams of ai to be used on 318 treated acres across 10 states at a rate of 5 grams ai per acre for a maximum of 5 applications. The application rate tested under GreenLight’s product performance protocol is a maximum of 4 grams ai/acre. However, GreenLight has requested a 25% overage beyond the intended application rate of Ledprona. The increased amount of ai requested accounts for the amount of ai needed to prime commercial sprayers and test application equipment prior to field use. The amount of ai requested is reasonable based the upper limit of the proposed labeled application rate intended for testing under the EUP that will be used for determining the rate of Ledprona recommended for a future commercial use label under a FIFRA Section 3 registration.

Table 2. Amount of Active Ingredient (AI) (Reproduced from Table 9 of MRID 51838501)

State	Total Treated Acres	Estimated maximum AI (g)
Idaho	1	20
Maine	62	1240
Michigan	22	440
Minnesota	42	840
New York	41	820
North Dakota	21	420
Oregon	23	460
Virginia	1	20
Wisconsin	62	1240
Washington	43	860
Total	318	6,360

Conclusions

We note that GreenLight's published information in Rodrigues, *et. al.* (2021) described small plot replicated field studies, including the testing of different potential application methods, competitive product comparisons, and developing IPM programs. This EUP will expand on that background work by Rodrigues, *et. al.* (2021) and, with the revised objectives one through six above, will potentially improve labeling associated with this product. Labelling improvements may be related to optimizing application rates, application timing, and clarifying directions of use. The requested acreage and amount of product, as well as the experimental protocols and methods proposed for testing the efficacy and product performance of Ledprona appear scientifically sound and are justified under section 5 of FIFRA for generating data to support registration of a pesticide product.

References

Rodrigues, T., Sridharan, K., Manley, B., Cunningham, D., & Narva, K. (2021, October 14). Development of dsRNA as a Sustainable Bioinsecticide: From Laboratory to Field. *American Chemical Society*, 65-82.

Environmental Protection Agency (EPA), 2022. Section G Experimental Use Program Review for 94614-EUP-R Assessing Ledprona (CAS# 2433753-68-3) Against Colorado Potato Beetle on Potatoes. Original Memorandum from M. Piombino to K. Welch through A. Reynolds and M. Mendelsohn, dated February 15, 2022.