EPA Review of Completed Carroll-Loye Study LNX-002

A field test of black fly repellency for two conditionally registered formulations containing 20% picaridin

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Organization of Presentation

- Background information
- Science Assessment
- Ethics Assessment

LNX-002: Basics

- Field test in one habitat of repellency of 2 picaridin repellents against biting flies
- 10 subjects treated with each repellent at dose rates established in earlier LNX-001
- 2 untreated subjects to confirm pest pressure
- Endpoint is first confirmed landing with intent to bite (Libe) for each subject

LNX-002: Protocol Review

- Protocol of 23 March 2009, was approved by IIRB, Inc. on 24 March and submitted to EPA by Carroll-Loye Biological Research
- EPA's science and ethics review of 18 May 2009 found the protocol acceptable with minor changes
- HSRB review on 25 June 2009 concurred with EPA but called for testing only with black flies or midges
- Amendment 1, 13 August 2009, addressed EPA and HSRB comments and was approved by IIRB, Inc. on 18 August 2009
- Amended protocol was approved by CDPR on 14 September 2009
- HSRB leadership on 16 September 2009 decided scope of amendment did not necessitate re-review by HSRB

LNX-002: Amendment 1

- Provides for collection & analysis of new dosimetry data on the cream
- As recommended by EPA
  - Corrects drafting error for stopping rules
  - Raises minimum landing pressure
  - Changes exposure from 5 of every 30 min to 1 of every 15 min
- As recommended by HSRB
  - Focuses test on black flies
  - Revises reference to 3rd-party insurance in consent form
- Revises discussion of how data censorship will be minimized
- Adds assay of subjects' attractiveness to target insects
- Revises protocol and consent form regarding number of subjects and details of subject participation

Study Execution

26-30 Sep 2009	Dose determination subjects recruited; dose determination testing with cream conducted
2 Mar 2010	Progress report submitted to IIRB, Inc.
9 Mar 2010	IIRB, Inc. approves one-year extension
15-19 Mar 2010	Subjects recruited for field test
20 Mar 2010	Field test conducted
1 Apr 2010	Deviation report to IIRB Re: use of superseded data collection form
5 Apr 2010	Study completion date
7 Apr 2010	Final report submitted to EPA

Study Reporting & Review

7 Apr 2010	Primary report of LNX-002 submitted to EPA
12 Apr 2010	EPA notified CLBR of missing record of IIRB, Inc. approval of Amendment 1
19 Apr 2010	CLBR submitted supplement including IIRB, Inc. approval of Amendment 1
7 Jun 10	CLBR submitted 2nd supplement reporting discovery that second black fly species not named in protocol had been present for field test

Documents Considered in EPA Reviews

- Primary Study Report MRID 48053802
- Supplement 1 Re: IIRB approval MRID 48071301
- Supplement 2 Re: Unnamed fly species MRID 48117601
- EPA Science & Ethics Review of Protocol LNX-002
- HSRB Report of June 2009 review of LNX-002
- CLBR supplemental submission of IIRB, Inc. roster and procedures

Science Assessment: LNX-002

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Objectives

- To test the black fly repellent efficacy of the test materials
- To satisfy a condition of registration imposed by EPA

Test Materials

- EPA Reg. No. 39967-50 (cream)
  39967-53 (pump spray)
- Both contain 20% Picaridin

LNX-002 Dose Determination

- Amendment 1 added a dose-determination phase with 15 additional subjects using the cream, to supplement the dosing data collected in study LNX-001
- The new and old dosing data for the cream were pooled to define the standard dose rate for the cream used in this study
- The standard dose rate for the spray was based on the data collected in LNX-001

LNX-002 Field Study Design

- 10 subjects treated with each formulation and 2 untreated control subjects participated in the one-day field trial in the Mojave desert
- Untreated subjects monitored black fly pressure; each attended by 2 technicians to aspirate landing insects
- Treated and untreated subjects' forearms were exposed to target insects for 1 minute at 15-minute intervals
- Duration of efficacy for each subject was measured as the time from treatment to "First Confirmed Landing with intent to bite" or "FCLibe"

Margins of Exposure

- Based on the mean surface area of treated arms and an assumed mean bodyweight of 70 kg, the highest picaridin dose administered (cream on arms) delivered a mean dose per subject of 2.86 mg/kg
- The limit dose for picaridin dermal toxicity in the rat is >2,000 mg/kg
- The margin of exposure (MOE) for dermal toxicity of the picaridin cream was at least 699
- Mean dose for pump spray on arms was 1.43 mg/kg; MOE ≥ 1399

Standard Doses and MOEs

	Mean Repellent Applied	Mean Picaridin applied	Mean Dose in 70-kg adult	MOE
Spray	0.5 g	100 mg	1.43 mg/kg	1399
Cream	1.0 g	200 mg	2.86 mg/kg	699

Statistical Analysis

- Data analyzed using Kaplan-Meier survival analysis
- Median CPT times were calculable for both product tests
- Mean CPT and time to 25% failure were also reported

Field Test Results: LNX-002

	Cream	Spray
Mean CPT ± sd (95% CI)	9.9 ± 2.0 h (8.5 - 11.4 h)	9.9 ± 1.5 h (8.8 - 11.0 h)
Kaplan-Meier Median CPT	10.1 h	9.8 h
Time to 25% failure	9.1 h	9.1 h

Role of Data Censorship

- 5 of the 10 subjects treated with the cream experienced a FCLIBe
- 6 of the 10 subjects treated with the spray experienced a FCLIBe
- Censored datapoints led to underestimates of the mean and sd, but did not compromise K-M medians
- Only three of the 9 subjects who did not experience failure received unconfirmed LIBes

Significance of Protocol Deviations

- Use of superseded data collection form
- Presence of unnamed black fly species *Simulium tescorum*
- 5½-month lapse between cream dose determination and field testing

Conclusions

- The study design and conduct meet EPA Guideline and Good Laboratory Practices standards
- The study results are sufficiently sound to support estimates of the duration of complete protection against black flies provided by
  - EPA Reg. No. 39967-50 KBR 3023 All-Family Insect Repellent Cream (20% picaridin cream)
  - EPA Reg. No. 39967-53 KBR 3023 All-Family Insect Repellent Spray (20% picaridin pump-spray)

Ethics Assessment: LNX-002

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Completeness of Submission

- The primary study report, MRID 48053802, is generally complete
- One deficiency noted:
  - No record of IIRB, Inc. approval of Amendment 1
  - Corrected by supplemental submission of MRID 48071301
- All requirements of 40 CFR 26.1303 for documentation of ethical conduct are satisfied by these two documents taken together

Protocol Deviations

- Three deviations:
  - Primary study report documents use of superseded data collection form
  - Supplemental report of 7 June 2010 documents presence of a second species of black fly at field test site
  - More than 60 days elapsed between dose determination and field testing
- None of these deviations affected the rights or safety of the subjects, or compromised informed consent

Response to Previous Ethics Reviews

- EPA's single comment in its protocol review of 18 May 09 was satisfactorily addressed in Amendment 1
- The HSRB's request for clarification of "what 3rd-party medical coverage means" was addressed in Amendment 1, but not ideally. CLBR added the words in red to clarify its promise to pay:

  "costs of such medical treatment that are not covered by your own insurance or by a third party that covers you"

  EPA now recommends:

  "costs of such medical treatment that are not covered by your own insurance or by the insurance of a third party under which you are covered"

Applicable Standards

- 40 CFR §26.1303, requiring documentation of the ethical conduct of the research
- 40 CFR §26.1703, forbidding EPA to rely on data from research involving intentional exposure of pregnant or nursing women or of children
- 40 CFR §26.1705, forbidding EPA to rely on data from research initiated after April 6, 2006 "unless EPA has adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part"
- FIFRA §12(a)(2)(P), which defines as unlawful "for any person . . . to use any pesticide in tests on human beings unless such human beings (i) are fully informed . . . and (ii) freely volunteer to participate in the test"

Findings

- The requirements of 40 CFR §26.1303 to document the ethical conduct of LNX-002 are satisfied
- LNX-002 did not involve intentional exposure of pregnant or nursing women or of children under 18
- Notwithstanding the minor deviations noted, LNX-002 was conducted in substantial compliance with all applicable requirements of 40 CFR part 26, subparts K and L
- Subjects were fully informed and participated voluntarily

Conclusion

- Assuming LNX-002 is determined to be scientifically acceptable, I find no barrier in law or regulation to EPA's reliance on it in actions under FIFRA

LNX-002: Charge Questions

1(a) Is the CLBR study LNX-002 sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against black flies provided by the tested repellents?

1(b) Does available information support a determination that study LNX-002 was conducted in substantial compliance with subparts K and L of 40 CFR Part 26?