EPA Review of Completed Carroll-Loye Study LNX-003

A laboratory test of the repellent efficacy against 2 tick species of 2 conditionally registered formulations containing picaridin

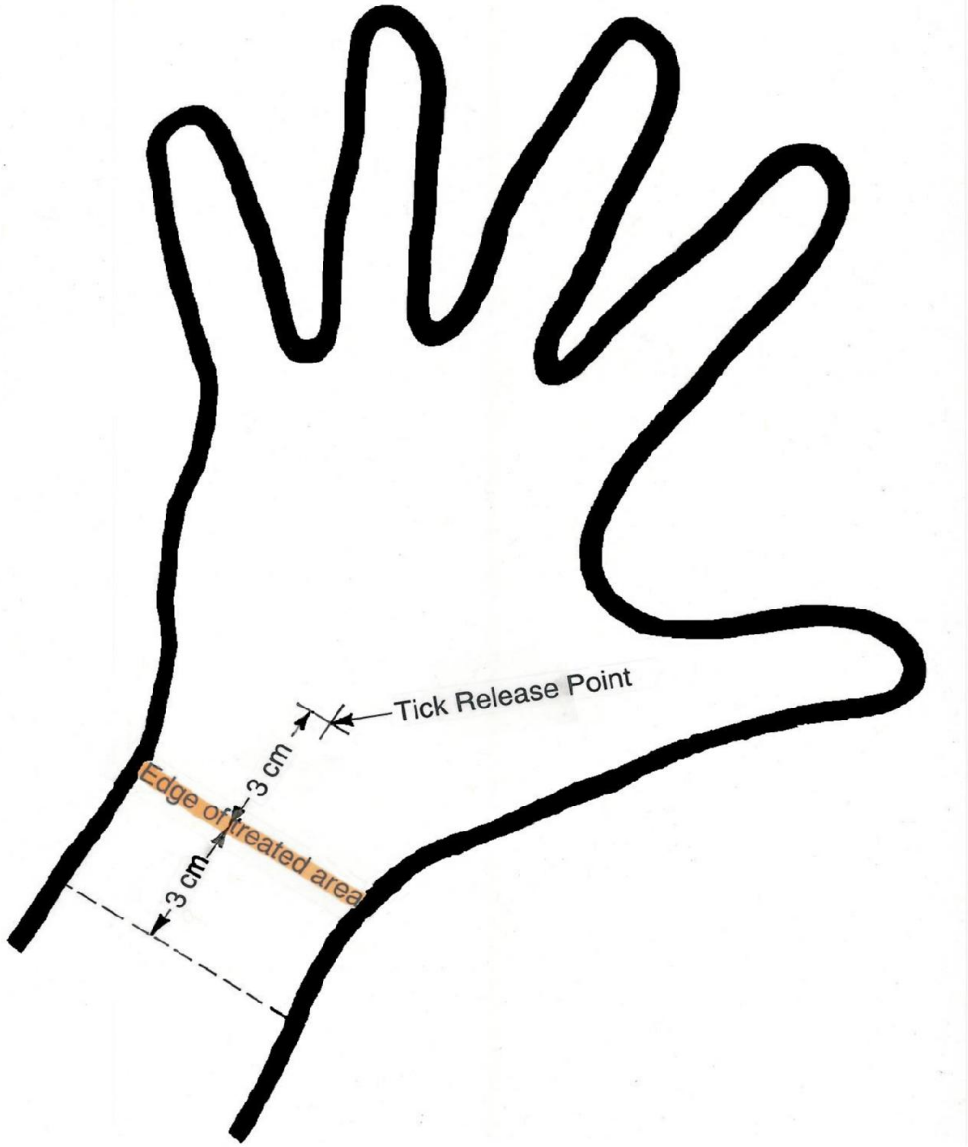
John M. Carley
Kevin Sweeney
Office of Pesticide Programs

Organization of Presentation

- Background information
- Science Assessment
- Ethics Assessment

LNX-003 Basics

- Laboratory test of repellency of 2 picaridin repellents against laboratory-reared, pathogen-free ticks of 2 species
- All subjects trained before study to handle ticks
- 20 subjects treated on one arm, 10 with each repellent, at standard dose rates established in earlier studies LNX-001 and LNX-002
- Untreated arm of each subject used to confirm tick aggressiveness and subject attractiveness


Tick Release Point
3 cm
Edge of treated area
3 cm
3 cm

LNX-003 Design

- In each exposure cycle, repeated every 15 min until end of study:
  - A tick of species A is tested for questing on untreated arm
  - Qualified tick of species A is tested for repellency on treated arm
  - A tick of species B is tested for questing on untreated arm
  - Qualified tick of species B is tested for repellency on treated arm
- Endpoint is first confirmed crossing for each tick species for each subject

LNX-003 Protocol Review

- Protocol LNX-003, 26 July 2009, was approved by IIRB, Inc. with a minor correction on 4 August 2009, and submitted to EPA on 6 August 2009
- The protocol met the standard of completeness defined in 40 CFR 26.1125
- EPA science and ethics review of 21 September 2009 was based on the initial protocol submission
- The HSRB reviewed protocol LNX-003 favorably at its meeting on 21 October 2009

Amendment 1, 30 October 2009

- Responds to EPA and HSRB comments and to initial California DPR review
- Clarifies
  - Procedures applying to one, both, or either tick species
  - Subject screening for attractiveness to ticks
  - Stopping rules
- Corrects minor errors and confusing statements
- Revises consent form and other documents

Review of Amendment 1

- Submitted to IIRB, Inc. on 2 November 2009
- Approved by IIRB, Inc. on 2 November 2009 after undocumented expedited review
- Amended protocol approved by California DPR on 16 November 2009

LNX-003 Execution & Reporting

7 January	Training ticks received from CDC
15-23 January	Subjects recruited and trained to handle ticks
20 January	Repellency ticks received from CDC
23-24 January	Repellency testing
5 April	Report completed
7 April	Report submitted

Science Assessment: LNX-003

Kevin Sweeney

Registration Division
Office of Pesticide Programs

Objectives

- To test the repellent efficacy of the test materials against nymphal ticks of 2 species
- To satisfy a condition of registration

Test Materials

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

LNX-003 Study Design

- 20 subjects and 3 alternates were trained in the laboratory to handle lab-reared, pathogen-free ticks and to remove them before they could bury and bite
- In efficacy trials
  - 10 subjects were treated with each test material
  - 10 subjects were tested on each of two successive days

LNX-003 Study Design—2

- The untreated arm of each treated subject served to ensure that only actively questing ticks were used in efficacy testing
- Each subject tested one nymphal tick of each species in each 15-minute exposure period, until efficacy failure or approximately 15 hours post-treatment
- Complete Protection Time (CPT) was calculated for each subject as the time from treatment to "First Confirmed Crossing" or "FCC"

Efficacy Doses and MOEs

	Mean Repellent Applied	Mean Picaridin Applied	Mean Dose in 70-kg adult	MOE
Spray	0.52 g	104 mg	1.49 mg/kg	1342
Cream	0.96 g	192 mg	2.74 mg/kg	730

Data Analysis and Censorship

- Spray product data provided enough information to calculate Kaplan-Meier median
- Data for cream product were too heavily right-censored to support calculation of median
- Mean CPT values and time to 25% failure reported for both products

Efficacy Test Results: LNX-003

		Cream	Spray
Ix. scapularis	Mean CPT ± sd (95% CI)	12.6 ± 4.3 h (9.5 - 15.7 h)	14.1 ± 1.8 h (12.7 - 15.4 h)
	Kaplan-Meier Median CPT	*	15.0 h
	Time to 25% failure	>15.4 h	13.1 h
D. variabilis	Mean CPT ± sd (95% CI)	15.3 ± 0.3 h (9.5 - 15.7 h)	14.0 ± 1.6 h (12.8 - 15.2 h)
	Kaplan-Meier Median CPT	*	14.1 h
	Time to 25% failure	9.7 h	12.0 h

* Insufficient data to calculate Kaplan-Meier Median CPT for Cream

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 *Dermacentor* and *Ixodes* ticks 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-003

John M. Carley

Human Research Ethics Review Officer
Office of Pesticide Programs

Documents Considered

- Primary study report MRID 48053801
- EPA Science & Ethics Review of Protocol LNX-003
- HSRB Report of October 2009 review of LNX-003
- IIRB, Inc. roster and procedures
- EPA—IIRB, Inc. e-mail exchange of 20 Apr 2010

Completeness

- The requirements of 40 CFR 26.1303 to document ethical conduct of the research are satisfied

Response to Previous Ethics Reviews

- In its 21 September 09 review of LNX-003 EPA called for:
  - Reclassification of two exclusion criteria as stopping rules
    - *Satisfactorily addressed in Amendment 1*
  - Revision of statement in consent form concerning payment for uninsured medical expenses
    - *Not addressed*
- In its 16 December 2009 final report of its October 2009 meeting the HSRB concurred with EPA's review and recommended no additional refinements to this protocol

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-003 have been satisfied
- LNX-003 did not involve intentional exposure of pregnant or nursing women or of children under 18
- There were no protocol deviations, and notwithstanding the failure to revise consent form language as directed by EPA, the overall record shows that LNX-003 was conducted in substantial compliance with all applicable requirements of 40 CFR part 26, subparts A-L
- Subjects were fully informed and participated voluntarily

Conclusion

- Assuming LNX-003 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-003: Charge Questions

2(a) Is the CLBR study LNX-003 sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against ticks provided by the tested repellents?

2(b) Does available information support a determination that study LNX-003 was conducted in substantial compliance with subparts K and L 40 CFR Part 26?