EPA Review of Completed Carroll-Loye Study SPC-002

A laboratory test of tick repellency for three registered formulations containing picaridin

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EPA and HSRB Protocol Review

- Protocol SPC-002 was approved by IIRB, Inc., on 17 Jul 07 and submitted to EPA by Carroll-Loye Biological Research in August 07
- The protocol submission met the standard of completeness defined in 40 CFR §26.1125
- EPA's science and ethics review of 24 Sept 07 was based on the initial protocol submission
- The HSRB reviewed protocol SPC-002 favorably at its meeting on 25 Oct 07

Post-HSRB Protocol Reviews

10 Jan 08	Draft final report of October HSRB
16 Jan 08	Amendment 1 submitted to IIRB, Inc.
22 Jan 08	Amendment 1 approved by IIRB, Inc.
26 Feb 08	CDPR initial review
28 Feb 08	Amendment 2 submitted to IIRB, Inc.
6 Mar 08	Amendment 2 approved by IIRB, Inc.
6 Mar 08	Final report of October HSRB
13 Mar 08	Protocol as amended approved by CDPR

Amendment 1: January 2008

- Identified CDC as source of ticks
- Described pathogen-screening of ticks
- Broadened scope of dose determination phase to include 2 towelette formulations
- Corrected description of 15% spray with sunscreen
- Clarified extrapolation plan for other formulations
- Added efficacy data collection form
- Appended draft label for 15% spray with sunscreen

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Amendment 2: Feb-March 2008

- Revised Consent Form (addressing EPA concerns)
- Revised Subjects' Bill of Rights
- Revised tick handling training sheet
- Appended MSDS for 15% spray with sunscreen
- Added treatment allocation form
- Revised tick crossing data capture form
- Added table to clarify extrapolation plan

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Study Execution and Reporting

15-19 Mar 08	Dose determination for SPC-001 and -002
22-23 Mar 08	Efficacy testing conducted for SPC-002
6 Jul 08	Deviation report to IIRB, Inc., Re: use of limb measurements from previous studies
	Study closeout report to IIRB, Inc.
14 Jul 08	IIRB, Inc. acceptance of deviation report and closeout report
19 Aug 08	Study report completed
9 Sep 08	Primary submission to EPA
7 Nov 08	Supplemental Submission to EPA

Science Assessment: SPC-002

Kevin Sweeney

Registration Division
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Elements in Science Review

- Dose Determination
- Efficacy Testing
- Conclusions

Dose Determination

- *Objective:*

  To estimate typical consumer dosing behavior for five repellent formulations containing picaridin:

  - 121-90 5.75% Towelette
  - 121-89 7% pump spray

  - 121-93 12% Towelette
  - 121-91 15% pump spray

  - 121-OT 15% pump spray with sunscreen

SPC-002 Dose Determination

- Dose determination conducted under protocol SPC-002 supported efficacy testing under both SPC-002 and SPC-001
- The dosimetry phase, with 10 subjects, established a typical consumer dose for each of five formulations
- The lower mean dose for each pair of “equivalent liquid formulations” was selected for use in efficacy testing

Typical Doses Determined for Equivalent Liquid Formulations

	Formulation	Grand Mean Dose
Arms	5.75% Towelette	1.38 ± 0.40 mg/cm^2
	7% Pump Spray	0.59 ± 0.32 mg/cm^2
	12% Towelette	1.26 ± 0.42 mg/cm^2
	15% Pump Spray	0.93 ± 0.50 mg/cm^2

Results of Dose Determination

Formulation	Standard Dose Rate (mg/cm^2)	
7% Pump Spray	Arms	0.59
	Legs	0.48
15% Pump Spray	Arms	0.93
	Legs	0.65
15% Pump Spray with SunScreen	Arms	0.75
	Legs	0.46

Efficacy Testing

Objectives:

- To measure Complete Protection Time (CPT) in the laboratory against two species of nymphal ticks afforded by three repellent formulations containing picaridin:
  - 121-89 7% pump spray
  - 121-91 15% pump spray
  - 121-OT 15% pump spray with sunscreen
- To satisfy a condition of registration imposed by EPA

SPC-002 Study Design

- 30 subjects were trained in the laboratory to handle lab-reared, pathogen-free ticks and to remove them before they could bury and bite
- 10 subjects were treated with each tested material
- Treatments were not distinguishable from each other; neither subjects nor technicians recording results knew who received which treatment
- 15 subjects were tested on each of two successive days

SPC-002 Study Design—2

- The untreated arm of each treated subject served as a control 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 as the mean time from treatment to “First Confirmed Crossing” or “FCC”

Efficacy Doses and MOEs

Formulation	Standard dose (mg/cm^2)		Average Picaridin applied	Dose rate (mg/kg)	MOE
7% Pump Spray	Arms	0.59	21.4 mg	0.302	6623
15% Pump Spray	Arms	0.93	74.4 mg	1.063	1881
15% Pump Spray with SunScreen	Arms	0.75	61.8 mg	0.883	2265

Efficacy Test Results: SPC-002

		7% Spray	15% Spray	15% SunSpray
Ixodes scapularis	Mean CPT ± SD (Range)	7.9 ± 1.4 h (6.5 - 9.3)	11.8 ± 3.3 h (8.5 - 15.2)	8.7 ± 4.3 h (4.5 - 13.0)
	Median CPT	8.25 h	----	8.25 h
	Mean crossings per subject	2.9 ± 1.1	1.4 ± 0.7	2.1 ± 1.2
Dermacentor variabilis	Mean CPT ± SD (Range)	5.7 ± 2.1 h (3.6 - 7.8)	9.7 ± 4.0 h (5.7 - 13.7)	8.2 ± 4.9 h (7.3 - 13.1)
	Median CPT	5.5 h	10.25 h	7.00 h
	Mean crossings per subject	2.4 ± 0.7	2.7 ± 1.7	2.5 ± 0.8

Protocol Deviation

- Some subject limb measurements on file from previous studies were used
- The same deviation was reported for study LNX-001, reviewed by HSRB in October 2008
- Deviation was reported to and accepted by IIRB, Inc.
- Deviation did not affect scientific integrity or results

Response to Comments in EPA Review

- The “lotion” product was inadequately characterized in the protocol
  - *Satisfactorily addressed in Amendment 1*
- Identify source of ticks, and describe how ticks are ensured to be disease-free
  - *Satisfactorily addressed in Amendment 1*

Response to HSRB Comment

In its 6 Mar 08 report the HSRB noted:

- Protocol SPC-002 did not rule out the same subject's testing more than one repellent, which would be inconsistent with the statistical design
  - *Addressed in Amendment 2 clarification of allocation of subjects to treatments*
  - *No subjects tested more than one repellent*

Conclusions

- The study provides scientifically valid results that meet EPA standards
- For purposes of labeling, the data are adequate to support claims of tick repellency as follows:
  - 7 hours for Reg. No. 121-89 Cutter Insect Repellent 7K (7% spray)
  - 11 hours for Reg. No. 121-91 Cutter Insect Repellent 15 KP (15% spray)
  - 8 hours for Reg. No. 121-OT Cutter Insect Repellent SS (15% spray with sunscreen)

Ethics Assessment: SPC-002

John M. Carley

Human Research Ethics Review Officer
Office of Pesticide Programs

Documents Considered

- Primary study report MRID 47535202
- CLBR supplemental submission of 7 Nov 08
- EPA science & ethics review of protocol 24 Sep 07
- HSRB Report of October 2007 review of protocol

Completeness

- MRID 47535202 as supplemented 7 Nov 08 meets the regulatory standard of completeness

Protocol Deviation

- Previously recorded limb measurements were used for some subjects
- This deviation was unintentional, was properly and timely reported to the IIRB, Inc., and was of no ethical consequence

Response to Previous Ethics Reviews

- In its 24 Sep 07 review of SPC-002 EPA called for:
  - Incorporation of an appropriate data collection form for recording efficacy test results
    - *Addressed in Amendment 1 and refined in Amendment 2*
  - Inclusion of product labels in protocol and provision to subjects in dose determination phase
    - *Draft label for 15% sunspray attached to protocol via Amendment 1*
  - Addressing in Consent Form risk of tick bites/disease and measures to prevent bites
    - *Addressed in Consent Form revisions with Amendment 2*
- In its 6 Mar 08 report the HSRB 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

- With the supplemental submission of 7 Nov 08, the requirements of 40 CFR §26.1303 to document the ethical conduct of SPC-002 are satisfied
- SPC-002 did not involve intentional exposure of pregnant or nursing women or of children under 18
- The only protocol deviation was unintentional, promptly reported, and of no ethical significance
- The overall record shows that SPC-002 was conducted in substantial compliance with the requirements of 40 CFR part 26, subparts A-L
- Subjects were fully informed and participated voluntarily

Conclusion

- Assuming SPC-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

SPC-002: Charge Questions

- Is the CLBR study SPC-002 sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy against ticks of the three formulations tested?

- Does available information support a determination that study SPC-002 was conducted in substantial compliance with subparts K and L 40 CFR Part 26?