EPA Review of Completed Carroll-Loye Study SPC-001

A field test of mosquito repellency for three registered formulations containing picaridin

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EPA and HSRB Protocol Review

- Protocol SPC-001 was approved by IIRB, Inc., 17 Jul 07 and submitted to EPA by Carroll-Loye Biological Research in August 07
- The initial 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-001 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.
6 Mar 08	Final report of October HSRB
16 May 08	Amendment 2 submitted to IIRB, Inc.
20 May 08	Amendment 2 approved by IIRB, Inc.
29 May 08	Protocol as amended approved by CDPR

Amendment 1: January 2008

- Broadened scope of dose determination phase to include 2 towelette formulations
- Corrected description of 15% repellent/sunscreen product
- Clarified extrapolation plan
- Clarified allocation of subjects to treatments

Amendment 2: May 2008

- Clarified terminology and language
- Added table to further clarify extrapolation plan
- Further clarified allocation of subjects to treatments
- Clarified timing of pregnancy testing
- Updated demographic description of the pool from which subjects were recruited

Study Execution and Reporting

15-19 Mar 08	Dose determination testing conducted under approved protocol SPC-002
8-14 Jun 08	Field testing conducted for SPC-001
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-001

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Dose Determination

- Typical consumer doses used in efficacy testing under protocol SPC-001 were determined in testing conducted under approved protocol SPC-002
- Protocol §6.1.4:
  - “Dosimetry data will be shared with the related repellent efficacy study detailed in the companion protocol SPC-002”

Efficacy Testing

Objectives

- To measure Complete Protection Time (CPT) in the field against mosquitoes 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-001 Study Design

- Similar to other recent Carroll-Loye field studies
- Subjects were trained in the laboratory to aspirate landing mosquitoes before they bite, using lab-reared, pathogen-free mosquitoes
- Treatments were not distinguishable in the field; neither subjects nor technicians recording results knew who received which treatment
- Untreated subjects monitored mosquito pressure; each was attended by 2 technicians to aspirate landing mosquitoes

SPC-001 Study Design—2

- 10 subjects treated with each formulation and 2 untreated control subjects participated in each of 2 field trials; some subjects participated on both days
- Both treated and untreated subjects were exposed to mosquitoes for 1 minute at 15-minute intervals, until efficacy failure or up to 17 hours post-treatment
- Complete Protection Time (CPT) was calculated as the mean time from treatment to “First Confirmed Landing with intent to bite” or “FCLibe”

Efficacy Dose Rates 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
	Legs	0.48	38.9 mg	0.556	3597
15% Pump Spray	Arms	0.93	74.4 mg	1.063	1881
	Legs	0.65	117.0 mg	1.671	1197
15% Pump Spray with SunScreen	Arms	0.75	61.8 mg	0.883	2265
	Legs	0.46	83.3 mg	1.189	1682

Field sites: California Central Valley

Date	Site	County	Habitat
8-Jun-08	1	Butte	Grassy lakeside with shrubs
14-Jun-08	2	Glenn	Tall native forest understory

Mosquito Species Distribution

Species	Site 1: 8 June 08		Site 2: 14 June 08	
	#	%	#	%
Aedes melanimon	145	65	125	45
Ae. vexans	23	10	44	16
Ae. increpitus	4	2	1	<1
Ae. sierrensis	7	3	19	7
Ae. nigromaculis	3	1	5	2
Culex tarsalis	15	7	37	13
Anopheles freeborni	19	8	38	14
An. punctipennis	1	<1		
An. franciscanus	7	3	7	3

Field Test Results: SPC-001

		7% Spray	15% Spray	15% SunSpray
Site 1 Butte County	Mean CPT ± SD (Range)	8.4 ± 2.1 h (6.3 - 10.5)	10.1 ± 4.0 h (6.1 - 14.1)	12.7 ± 4.9 h (7.8 - 17.6)
	Median CPT	9.4 h	10.3 h	13.3 h
	Mean LIBes/subject	2.6 ± 0.7	2.5 ± 0.5	3.2 ± 0.8
Site 2 Glenn County	Mean CPT ± SD (Range)	7.0 ± 2.2 h (4.8 - 9.2)	10.7 ± 0.8 h (9.9 - 11.5)	10.9 ± 0.8 h (10.1 - 11.7)
	Median CPT	7.4 h	10.4 h	11.7 h
	Mean LIBes/subject	2.8 ± 0.6	2.4 ± 0.7	2.7 ± 1.2

Protocol Deviation

- Same deviation reported for study LNX-001, reviewed by HSRB in October 2008, and for SPC-002: use of subject limb measurements on file from previous studies
- Deviation was reported to and accepted by IIRB, Inc.
- Deviation did not affect scientific integrity or results

Response to Comment in EPA Review

- EPA review of 24 Sep 2007 noted that the "lotion" product was inadequately characterized in the protocol
  - *The description of the 15% pump spray with sunscreen, added to the protocol through Amendment 1, satisfactorily addressed this concern*

Conclusions

- The study provides scientifically valid results that meet EPA standards
- For purposes of labeling this study supports claims of repellency as follows:
  - 8 hours for Reg. No. 121-89 Cutter Insect Repellent 7K (7% spray)
  - 10 hours for Reg. No. 121-91 Cutter Insect Repellent 15 KP (15% spray)
  - 12 hours for Reg. No. 121-OT Cutter Insect Repellent SS (15% spray with sunscreen)

Ethics Assessment: SPC-001

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Office of Pesticide Programs

Documents Considered

- Primary study report MRID 47535201
- 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 47535201 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 EPA & HSRB Ethics Reviews

- In its 24 Sep 07 protocol review EPA called for:
  - Incorporation of an appropriate data collection form for recording field test results
    - *Mentioned in summary of Amendment 1, but not attached to protocol*
    - *An appropriate form was used in study*
  - Inclusion of product labels in protocol and provision to subjects in dose determination phase
    - *Label for 15% sunspray attached to protocol via Amendment 1*
- In its 6 Mar 08 report on its review of this protocol, the HSRB made no additional recommendations for refinements

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-001 are satisfied
- SPC-001 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-001 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-001 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-001: Charge Questions

- Is the CLBR study SPC-001 sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy against mosquitoes of the three formulations tested?

- Does available information support a determination that study SPC-001 was conducted in substantial compliance with subparts K and L 40 CFR Part 26?