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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

20 May 2010

MEMORANDUM

SUBJECT: Ethics Review of Completed Carroll-Loye Black Fly Repellent Field Efficacy Study LNX-002

FROM: John M. Carley
Human Research Ethics Review Officer
Office of Pesticide Programs

TO: Marion Johnson, Chief
Insecticides Branch
Registration Division

REF: Carroll, S. (2010) Efficacy Test of KBR 3023 (Picaridin; Icaridin)-based Personal Insect Repellents (20% Cream and 20% Spray) with Black Flies under Field Conditions. Unpublished study prepared by Carroll-Loye Biological Research under Project No. LNX-002. 331 p. (MRID 48053802)

Carroll, S. (2010) Efficacy Test of KBR 3023 (Picaridin; Icaridin)-based Personal Insect Repellents (20% Cream and 20% Spray) with Black Flies under Field Conditions: Supplemental Submission to EPA MRID 48053802. Project Number: LNX-002-1. Unpublished study prepared by Carroll-Loye Biological Research. 6 p. (MRID 48071301)

I have reviewed all available information concerning the ethical conduct of the research reported in the referenced documents, which describe the execution of Carroll-Loye protocol LNX-002. If it is determined to be scientifically acceptable, I find no barrier to EPA's reliance on this study.

Background and Chronology

The protocol LNX-002 was initially submitted to EPA for review in April 2009. The protocol and EPA's review of 18 May 2009 were discussed by the HSRB on 25 June 2009. The HSRB reviewed the protocol favorably, concluding in their 26 October

2009 final report of the June meeting that "the proposed study is likely to meet the applicable ethical requirements for research involving human participants."

Following the HSRB review, the protocol and consent form were modified through Amendment 1 of 13 August 2009. This amendment incorporated changes responsive to the comments of EPA, the HSRB, and California Department of Pesticide Regulation (CDPR), as well as additional corrections initiated by the investigators and, at the request of the sponsor, provision for collecting additional dose-determination data for the cream formulation, to be pooled with that originally collected in study LNX-001. The Independent Investigational Review Board, Inc. granted approval to Amendment 1 and supporting documents on 18 August 2009.[1]

Because the study was to be conducted in California, the approval of CDPR was also required before the study could be initiated. CDPR granted final approval of the amended protocol and supporting documents 14 September 2009.

The dose determination phase of LNX-002 was conducted from 26-30 September, 2009, and by EPA's definition, 26 September—the date of enrollment of the first subject—was the "study initiation date."[2] As the expiration date of the initial IRB approval approached in March 2010, the investigators sent an application for renewal to the IRB on 2 March 2010. The IIRB, Inc. renewed their approval effective 9 March 2010.

Subjects for the field study were enrolled 15-19 March, 2010, and the field study was conducted on 20 March 2010. The study report was completed on 5 April 2010, and submitted to EPA by the sponsor, Lanxess, on 7 April 2010. A full chronology appears as Attachment 2 to this review.

Scope of Review:

This review reflects consideration of the primary study report and supplement cited above, and the following additional documents:

- Supplemental submissions of IIRB, Inc. roster (as of 10 January 2010) and of IIRB, Inc. procedures (as of 1 October 2009)
- EPA's 18 May 2009 Science and Ethics Review of Protocol LNX-002
- The HSRB's 26 October 2009 report of its June 2009 discussion of LNX-002

[1] Documentation of official notification to the sponsor and investigator of IIRB, Inc., approval of Amendment 1 is not included in the primary study report. CLBR was notified of this deficiency on April 12, 2010, and provided the missing documentation in the cited supplemental report on April 19, 2010.
[2] On the title page the "Study Initiation Date" is shown as 23 March 2009. This is, in fact, the version date of the protocol reviewed by EPA and the HSRB.

Completeness of Submission:

The checklist used by EPA to verify satisfaction of the requirements of §26.1303 as they apply to the report of LNX-002 appears as Attachment 1 to this review. Taking into account the supplemental submission documenting IRB approval of Amendment 1, all requirements of §26.1303 were satisfactorily addressed.

Protocol Deviations:

One deviation from the amended protocol is reported on p. 260: a preliminary version of the repellency data collection form bearing an incorrect title was used inadvertently. I concur with the investigator that this deviation had no effect on data quality or subject safety.

In addition to this reported deviation from the protocol, there was another, unacknowledged deviation. The protocol as amended states at §3.2 "Recruitment for the Dosimetry study is conducted within a 60-day period prior to the repellency field test day." (p. 175, lines 418-419) In fact, recruitment for the dose-determination phase was conducted in September, 2009, almost 6 months before the repellency field test day. There is no obvious reason why it would be important to conduct dose determination testing within 60 days of field testing, and I conclude that this deviation also could not have had an effect on data quality or subject safety.

Applicable Ethical Standards

Because this study was initiated after 7 April 2006, prior submission of the protocol and supporting materials to EPA was required by 40 CFR §26.1125. 40 CFR §26.1601(c) required EPA to review the protocol and present it to the HSRB for review.

- *Prior EPA and HSRB Reviews*

In its Science and Ethics review of 18 May 2009 EPA identified no deficiencies requiring correction relative to 40 CFR 26, subparts K and L, or to FIFRA §12(a)(2)(P). That review did note and suggest editorial correction of a misplaced criterion for stopping the test.

The protocol LNX-002 was discussed by the HSRB on 25 June 2009. In its 26 October 2009 final report of that discussion the HSRB concurred with EPA's review, and added:

> The Board recommended that the investigators clarify what "3rd party" medical coverage means, as listed in the current informed consent document.

- *Regulatory and Statutory Standards*

The following provisions of 40 CFR 26 Subpart Q, as amended effective August 22, 2006, define the applicable ethical standards, which read in pertinent part:

> §26.1703: Except as provided in §26.1706, . . . EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.
>
> §26.1705: Except as provided in §26.1706, . . . EPA shall not rely on data from any research initiated after April 7, 2006, unless EPA has adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part. . . .

In addition, §12(a)(2)(P) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) applies. This passage reads:

> In general, [i]t shall be unlawful for any person . . . to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test.

Findings

- *Protocol Review by EPA and HSRB*

The requirements of 40 CFR §26.1125 for prior submission of the protocol to EPA and of §26.1601 for HSRB review of the protocol were satisfied.

- *Responsiveness to EPA and HSRB reviews*

EPA's suggestion in its review of 18 May 2009 was addressed satisfactorily in Amendment 1. The reference to 3rd party coverage of costs of medical treatment noted by the HSRB was revised in Amendment 1.

- *Prohibition of research involving intentional exposure of pregnant or nursing women or of children*

All female subjects in both the dose-determination and repellency phases of the research were administered over-the-counter pregnancy tests on the day of exposure to the repellents; all such tests were negative. All female subjects told investigators they were not nursing. All subjects were over 18. Thus the prohibition in 40 CFR §26.1703 of research involving intentional exposure of pregnant or nursing women or of children under 18 was satisfied.

- *Substantial compliance with 40 CFR 26 subparts A through L*

40 CFR §26.1705 requires that EPA have "adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part." Within this range, only subparts K and L are directly applicable to the conduct of third-party research.

The two noted deviations from the protocol were minor, with no possible effect on the integrity of the research or the safety of subjects. Taking into account the overall care with which the research was defined and conducted, these minor deficiencies in the conduct of the research fall far below the level of substantial non-compliance with subparts A through L of 40 CFR part 26. I conclude that 40 CFR §26.1705 does not prohibit EPA reliance on this study.

- *Compliance with 40 CFR §26 subpart M*

As is documented in Attachment 1 to this memorandum, the primary study report failed to address the requirement of 40 CFR §26 subpart M, §26.1303(b) to submit copies of "official notification to the sponsor or investigator . . . that research involving human subjects has been reviewed and approved by an IRB." This omission was corrected by the submission of a supplemental document catalogued as MRID 48071301. Taking the two submissions together, along with the separately submitted documents reporting the roster and procedures of the IIRB, Inc., the requirements of 40 CFR §26.1303 to document the ethical conduct of the research were fully satisfied.

- *Compliance with FIFRA §12(a)(2)(P)*

The requirement of FIFRA §12(a)(2)(P) that human subjects of research be "fully informed of the nature and purposes of the test and of any physical and mental health consequences reasonably foreseeable therefrom," and "freely volunteer to participate in the test," was met for this study.

Conclusions

This study reports research conducted in substantial compliance with the requirements of 40 CFR 26 subparts A through L. In its conduct it met all applicable ethical standards for the protection of human subjects of research. An initial omission in reporting was promptly corrected, and all requirements for documentation of ethical conduct of the research were satisfied. If this study is determined to be scientifically valid and relevant, there is no regulatory barrier to EPA's reliance on it in actions under FIFRA or §408 of FFDCA.

Attachment 1: §26.1303 completeness check for LNX-002
Attachment 2: Chronology of CLBR LNX-002

§ 26.1303 Check for Completeness of Reports of Human Research Submitted for EPA Review
CLBR Study No. LNX-002: MRIDs 48053802 and 48071301

Any person who submits to EPA data derived from human research covered by this subpart shall provide at the time of submission information concerning the ethical conduct of such research. To the extent available to the submitter and not previously provided to EPA, such information should include:

Requirement			Y/N	Comments/Page References
(a) Copies of all of the records relevant to the research specified by §26.1115(a) to be prepared and maintained by an IRB	§1115(a)(1): Copies of • all research proposals reviewed, • scientific evaluations, if any, that accompany the proposals, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.		Y n/a Y Y	Initially addressed in protocol; Amendment 1 pp. 226-237. Final approved CFs pp. 239-258. Progress Report pp. 317-321
	§1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		Y	Minutes of IIRB review of Amendment 1 pp. 312-315.
	§1115(a)(3): Records of continuing review activities.		Y	pp. 316, 329
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.		Y	pp. 264-329
	§1115(a)(5): • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.		Y	1/21/2010 roster in supplement
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).		Y	10/1/2009 procedures in supplement
	§1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5).		n/a	
(b) Copies of all of the records relevant to the information identified in §26.1125(a)-(f)	§1125(a) A discussion of:	(1) The potential risks to human subjects;	Y	Addressed in protocol
		(2) The measures proposed to minimize risks to the human subjects;	Y	Addressed in protocol
		(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue;	Y	Addressed in protocol
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	Addressed in protocol
		(5) The balance of risks and benefits of the proposed research.	Y	Slightly revised p. 172
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	Revised CFs pp. 195-214; final approved CFs pp. 239-258
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	Satisfied in protocol
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.		Y	Satisfied in protocol
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	See §1115(a)(4) above
	§1125(f): Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB.		Y	IRB approval of Amendment 1 documented in MRID 48071301. Final CDPR approval p. 263
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research			Y	pp. 239-258
(d) If any of the information listed in paragraphs (a) through (c) of this section is not provided, the person shall describe the efforts made to obtain the information.			n/a	

Chronology of CLBR LNX-002

23 Mar 2009	Date of protocol submitted for EPA and HSRB review
24 Mar 2009	Initial IIRB, Inc. protocol approval
18 May 2009	EPA protocol review
2 Jun 2009	Initial CDPR review
25 Jun 2009	HSRB protocol discussion
26 Oct 2009	Final report of HSRB protocol review

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13 Aug 2009 Amendment 1

- Provides for collection and analysis of additional dosimetry data on the 20% Cream
- Corrects drafting error noted by EPA
- Clarifies reference to 3rd-party insurance coverage in consent form
- Raises threshold of acceptable minimum landing pressure as recommended by EPA
- Changes exposure pattern from 5 minutes of every 30 to one minute of every 15
- Focuses the field efficacy test on black flies as recommended by HSRB
- Revises discussion of how data censorship will be minimized
- Adds assay of subjects' attractiveness to the target insects
- Revises protocol and consent form regarding number of subjects recruited and details of subject participation

18 Aug 2009	IIRB Approval of Amendment 1
14 Sep 2009	CDPR Approval of Amendment 1
26 Sep 2009	First subject enrolled (Experimental Start Date)
26-30 Sep 2009	Dose determination testing
2 Mar 2010	CLBR progress report submitted to IIRB
9 Mar 2010	IIRB approves renewal for one year
15-19 Mar 2010	Subject recruiting for field efficacy phase
20 Mar 2010	Efficacy Field Testing (Experimental End Date)
1 Apr 2010	Deviation Report
5 Apr 2010	Study Completion Date
7 Apr 2010	Study Submission Date
12 Apr 2010	EPA notification of missing IIRB approval notice
19 Apr 2010	Supplemental submission of IIRB approval of Amendment 1