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 Tick Repellent Laboratory Efficacy Study LNX-003

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

TO: Marion Johnson, Chief
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REF: Carroll, S. (2010) Efficacy Test of KBR 3023 (Picaridin; Icaridin)-based Personal Insect Repellents (20% Cream and 20% Spray) with Ticks under Laboratory Conditions. Unpublished study prepared by Carroll-Loye Biological Research under Project No. LNX-003. 168 p. (MRID 48053801)

I have reviewed all available information concerning the ethical conduct of the research reported in the referenced document, which reports the execution of Carroll-Loye protocol LNX-003. 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-003 was initially submitted to EPA for review in August 2009. The protocol and EPA's review of 21 September 2009, as well as a supplemental submission from the investigators promising revisions to address EPA comments, were presented to the HSRB on 21 October 2009. The HSRB reviewed the protocol favorably, concluding in their 16 December 2009 report of the October meeting that "the proposed laboratory tick repellency study protocol LNX003, if modified in accordance with EPA (Sherman and Sweeney 2009) recommendations, and performed as described, will likely meet the applicable requirements of 40 CFR 26, subparts K and L."

After the HSRB review, the protocol and consent form were modified through Amendment 1 of 30 October 2009. This amendment incorporated changes responsive to the comments of EPA, the HSRB, and California Department of Pesticide Regulation (CDPR), as well as some additional corrections initiated by the investigators.

The amendment was sent to the Independent Investigational Review Board, Inc., on 2 November 2009. IIRB's 2 November 2009 approval of Amendment 1 (p. 160) characterized all changes as "administrative", and thus "minor changes in previously approved research" eligible for expedited review.[1]

Because the study was to be conducted in California, the approval of the California Department of Pesticide Regulation was also required. CDPR granted final approval of the amended protocol and supporting documents on 16 November 2009.

Subjects were recruited 15-23 January 2010, and by EPA's definition, 15 January 2010—the date of enrollment of the first subject—was the "study initiation date."[2] The repellency study was conducted on 23-24 January 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 cited above, and the following additional documents:

- Supplemental submissions of IIRB, Inc. roster (as of 10 January 2010) and of IIRB, Inc. Human Research Protection Program Plan (as of 1 October 2009)

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[1] CLBR requested (p. 161) a copy of IIRB minutes of meeting at which Amendment 1 was approved. IIRB's response (p. 161) says "it was approved through expedited procedures and not at a convened meeting; therefore, there are not meeting minutes for that transaction."

The IIRB's Human Research Protection Program Plan effective 1 October 2009 requires an Expedited Reviewer to document the review, and the full Board to review a summary of expedited review actions at a convened meeting. EPA requested any available documentation from IIRB, Inc. on 20 Apr 2010; IIRB responded on 20 Apr 2010 with such documentation as there is of the amendment review.

IIRB's characterization of the amendments as "minor changes in previously approved research" eligible for expedited review may have been appropriate; their characterization of all the amendments as "administrative" was not. The amendments made substantive changes in both the protocol and the consent form affecting what subjects were told and how their welfare was protected. The absence of any record of the substance of the IIRB review makes impossible any assessment of the IRB's compliance with its own procedures as defined in its HRPP Plan.

[2] On the title page of the completed study report the "Study Initiation Date" is shown as 26 July 2009, the date of signature on the un-amended protocol by the Study Director, consistent with the definition of study initiation in EPA's Good Laboratory Practice (GLP) rules. For purposes of the human study rule, however, EPA defines study initiation as the enrollment of the first subject; for this study that occurred on 15 January 2010.

- EPA-IIRB, Inc., email exchange of 20 April 2010 concerning additional documentation of IRB review of Amendment 1
- EPA's 21 September 2009 Science and Ethics Review of Protocol LNX-003
- The HSRB's 16 December 2009 final report of its October 2009 discussion of LNX-003

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-003 appears as Attachment 1 to this review. All requirements of §26.1303 were satisfactorily addressed.

Protocol Deviations:

The investigator reported no deviations from the amended protocol (p. 154) and none were found.

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 21 September 2009 EPA identified two deficiencies requiring correction before study execution: further clarification of the statement in the consent form concerning payment of uninsured medical expenses, and reclassification of two "exclusion criteria" as stopping rules.

The protocol LNX-003 was discussed by the HSRB on 21 October 2009. In the 16 December 2009 final report of this discussion the HSRB concurred with EPA's review, and did not recommend any additional changes.

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 call for specific changes to the Consent Form language concerning payment of costs of medical treatment not reimbursed by insurance was not addressed; the protocol as amended and executed did not incorporate either the specified language or any other change from the proposal. This statement, however, reflected changes made in the consent form used in study LNX-002 in response to a comment on that study proposal by the HSRB.

EPA's call for reclassification of two "exclusion criteria" as stopping rules was implemented in Amendment 1.

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

All female subjects in 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 requirements of 40 CFR §26.1703 were 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 failure to implement the specific change of wording called for in EPA's protocol review was a minor deficiency. Taking into account the overall care with which the research was defined and conducted, it falls 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*

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. 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-003
Attachment 2: Chronology of CLBR LNX-003

§ 26.1303 Check for Completeness of Reports of Human Research Submitted for EPA Review
CLBR Study No. LNX-003: MRID 48053801

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 n/a	Initially addressed in protocol; Amendment 1 pp. 135-144. Final approved CFs pp. 145-153.
	§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.		n/a	Minutes of initial IRB review were provided with protocol Amendment 1 approved per expedited review; no IRB minutes were made
	§1115(a)(3): Records of continuing review activities.		n/a	
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.		Y	pp. 157-166
	§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 HRPP Plan 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	Satisfied in protocol
		(2) The measures proposed to minimize risks to the human subjects;	Y	Satisfied in protocol
		(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue;	Y	Satisfied in protocol
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	Satisfied in protocol
		(5) The balance of risks and benefits of the proposed research.	Y	Satisfied in protocol
	§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. 135-144; final approved CFs pp. 145-153
	§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 p. 160 Final CDPR approval p. 156
(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. 145-153
(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-003

26 Jul 2009	Protocol date
27 Jul 2009	Protocol submitted to IIRB, Inc.
28 Jul 2009	Date of IIRB approval on CF p. 125 et seq. (/s/ in protocol)
30 Jul 2009	IIRB approval letter noting discrepant date for subject training
3 Aug 2009	CLBR correction of date discrepancy noted by IIRB
4 Aug 2009	IIRB approval of CLBR correction of error
6 Aug 2009	Informal protocol submission to EPA
24 Aug 2009	Formal protocol submission to EPA
31 Aug 2009	Preliminary EPA comments on protocol provided to CLBR
8-10 Sep 2009	First redline changes to protocol by CLBR.
16 Sep 2009	CLBR supplemental submission describing planned amendments to protocol and soliciting EPA comments
21 Sep 2009	EPA Science & Ethics Review of Protocol and CLBR Supplement
20 Oct 2009	Further redline changes to protocol by CLBR
21 Oct 2009	HSRB Review
16 Dec 2009	Final Report of October HSRB Meeting

26-28 Oct 2009	Further redline changes to protocol by CLBR
29 Oct 2009	Redline changes to CF by CLBR
30 Oct 2009	Amendment 1

- Responds to EPA and HSRB comments and to review by California DPR
- Clarifies how procedures apply to one, both, or either tick species
- Clarifies how subjects are screened for attractiveness to target ticks
- Clarifies stopping rules
- Corrects minor errors and confusing statements
- Revises consent form and other support documents

2 Nov 2009	Amendment 1 transmitted to IIRB, Inc.
2 Nov 2009	IIRB, Inc. approval of Amendment 1 after expedited review
3 Nov 2009	IRB endorsement of expedited approval of Amendment 1
16 Nov 2009	CDPR Approval of Amendment 1
7 Jan 2010	Ticks used for subject training received from CDC
15 Jan 2010	First subject enrolled (Experimental Start Date)
15-23 Jan 2010	Subject recruitment

20 Jan 2010	Ticks used for efficacy testing received from CDC
23-24 Jan 2010	Efficacy testing
24 Jan 2010	Experimental End Date
5 Apr 2010	Study Completion Date
7 Apr 2010	Submission to EPA
20 Apr 2010	EPA-IIRB email exchange concerning documentation of expedited review of Amendment 1