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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

September 23, 2008

MEMORANDUM

SUBJECT: Ethics Review of Completed Carroll-Loye Field Mosquito Repellent Efficacy Study LNX-001

FROM: John M. Carley
Human Research Ethics Review Officer
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TO: Marion Johnson, Chief
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REF: Carroll, S. (2008) Efficacy Test of KBR 3023 (Picaridin; Icaridin)-based Personal Insect Repellents (20% Cream and 20% Spray) with Mosquitoes under Field Conditions. Unpublished study prepared by Carroll-Loye Biological Research under Project No. LNX-001. 339 p. (MRID 47506401)

I have reviewed all available information concerning the ethical conduct of the research reported in the referenced document, which describe the execution of Carroll-Loye protocol LNX-001.

The protocol LNX-001 was initially submitted to EPA for review in April 2007. In response to EPA's review of May 24, 2007, the protocol was amended and the single consent form was divided into two—one for treated subjects and another for untreated control subjects. These revisions were approved by the IRB on June 12, 2007 and submitted to EPA and the HSRB docket on June 14, 2007. The protocol and these amendments were reviewed favorably by the Human Studies Review Board at its meeting in June 2007. In the December 18, 2007 final report of its June meeting the HSRB concluded that, as amended, "the protocol meets the applicable requirements of 40 CFR

26, subparts K and L," and made no recommendations for further changes in the protocol from an ethics perspective.

Because the study was to be conducted in California, the approval of the California Department of Pesticide Regulation (CDPR) was required before the study could be initiated. CDPR requested minor changes in the consent forms, and approved the amended proposal in January 2008. As the expiration date of the initial IRB approval approached in March 2008, the investigators recruited two subjects to participate in LNX-001, and sent their signed consent forms to the IRB with their application for renewal. After a final round of amendments approved by the IRB on April 28, 2008, subjects were recruited, the preliminary dose-determination phase of the study was conducted May 14-23, 2008, and the field study was conducted on June 7 and 15, 2008. The study report was completed on August 5, 2008, electronically submitted to EPA informally on August 7, 2008, and formally submitted to EPA by the sponsor, Lanxness, on August 12, 2008.

Scope of Review:

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

- EPA's protocol review of May 24, 2007
- The HSRB's December 18, 2007 report of its June 2007 discussion of LNX-001
- An exchange of e-mail between John Carley of EPA and Scott Carroll and Shawn King of Carroll-Loye Biological Research (8/8/08-9/10/08) clarifying reporting of the time of treatment of subjects on June 7.

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-001 appears as Attachment 1 to this review. Most requirements were satisfactorily addressed. The following exceptions were noted:

- Correspondence included in the study report suggests that the protocol and consent forms were amended in October 2007 in response to comments from CDPR. If such an IRB review cycle occurred, it is not documented except by the inclusion of two revised consent forms (pp. 249-266) with tracked changes, not showing evidence of IRB approval.

- 40 CFR §26.1303(a) requires submission of, among other records of IRB review specified in §26.1115(a), "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." No minutes of any of the IRB meetings were included in the study report, nor was any explanation provided for their absence.

The record of correspondence with the IRB appears to be fairly complete, but because e-mail documents transmitting reports, amendments, etc., were separated from the transmitted documents it is difficult to be certain. Attachment 2 to this review supplements the table of contents on pp. 4-5 of the study report with an annotated listing of specific documents included in Appendix 7 to the study report.

Protocol Deviations

Three deviations from the protocol are reported on pp. 206-207.

- *"Carroll-Loye Biological Research staff member failed to sign the Informed Consent Form (ICF) for one of two test subjects enrolled 23 Mar 2008 prior to scanning the document for electronic submission to IIRB."*

  A Deviation Report (p. 269) was prepared on 31 March 2008 and transmitted to IIRB, Inc., on the same date (pp. 229-230). IIRB, Inc. accepted the deviation report on 4 April 2008 (p. 271).

  These two subjects were recruited in March so that signed consent forms—on one each of the two separate forms for treated and for untreated subjects—could be included with the investigator's application for renewal of IIRB approval of the research. Haste to comply with what was misunderstood to be a requirement of the IRB led to an error. At the recommendation of IIRB staff, the subjects who had signed the early consent were reported as "screening failures", and were re-recruited. One participated in the testing, after signing the appropriate consent form as later amended and approved by the IIRB on April 28, 2008. The other did not participate, because of a schedule conflict. This deviation had no substantive impact on the eventual conduct of the research, on the health or safety of the subject involved, or on the integrity of the informed consent process.

- *"Following discussions with the U.S. Environmental Protection Agency regulatory personnel, we implemented a practice of using on-file limb measurements for subjects who had participated in previous studies and been measured within the last two years and who also responded in the negative when asked verbally if they had gained or lost muscle mass or other weight in the interim. We neglected to amend the protocol to specify this change, and therefore it constitutes a deviation."*

A Deviation Report (p. 266) was prepared on 6 July 2008 and transmitted to IIRB, Inc., on 16 July 2008 (p. 245). IIRB, Inc. accepted the deviation report on 21 July 2008 (p. 282).

I concur with the Study Director that "this practice reduced the invasiveness of our testing procedures for repeat subjects." It also streamlines the procedure in a reasonable way. But this was clearly a thoughtful, planned change in the protocol that was not required to eliminate an apparent immediate hazard to the subjects, and by rule it should have been made only by amendment, approved by the IRB before it was implemented.

- *"Amendment 2 was submitted 17 August 2007 to IIRB, Inc., but was not received . . . . The amendment was a single-word correction to bring the language in the Protocol into agreement with the language in the already approved Informed Consent Form . . . . Since the protocol was executed without making the change, the unfulfilled need for this editorial correction constitutes a minor protocol deviation. The protocol as submitted to the Quality Assurance Unit and to the Sponsor as addendum to the final study report will include this editorial change for accuracy."*

  A Deviation Report (p. 280) was prepared on 20 July 2008 and transmitted to IIRB, Inc., on 21 July 2008 (p. 247). IIRB, Inc. accepted the deviation report on 21 July 2008 (p. 282).

  The email record provided shows that Amendment 2 was initially transmitted to IIRB on 15 August 2007 (p. 218). The following day IIRB, Inc. responded that they had not received the attachments (p. 219), and requested re-transmittal. Then on 17 August, CLBR retransmitted the original email message. It is unclear from the reported email traffic whether the amendment was attached to either CLBR message. Neither IIRB, Inc., nor CLBR followed up until after the research had been initiated. IIRB, Inc. ultimately approved Amendment 2 after the field phase of the study had been completed.

  I concur with the Study Director that "subjects were provided the correct characterization of the test materials in the consenting documents used in enrollment, so the deviation did not affect subject safety or rights. Data integrity was not affected."

In addition to these three reported deviations from the protocol, there was another. The protocol states at §10.3 (p. 154) "The time at which the application of a treatment is completed is recorded as t_0 ('time zero')." At §1.4.6 (p. 157) it states "the time of application is recorded for each subject." Consistent with the protocol, the time of application for each subject is reported on p. 114 for field study day 2, June 15, at Howard Slough. On that day, it took three technicians 40 minutes to treat all 20 subjects. But the time of application for all 20 treated subjects on field study day 1, June 7, at Gray

Lodge is recorded as 08:00. In response to an email request for clarification, the Study Director responded in an email on 5 September 2008:

> *On the first day of the study, however, we inadvertently adhered to our [past practice] and recorded a mean application time of 0800 for a series of applications made by four technicians between, approximately, 0745-0810. On the second test day, we recorded actual application times, and for even greater completeness, included technician initials for the first time as well.*
>
> *Our practice on the first day was thus a minor protocol deviation that we did not note as such at the time, and hence did not report to the IRB. The implications of this deviation for the data set or the subjects' rights and safety appear small.*

In a subsequent email on 10 September 2008 the CLBR Director of Operations reported that a deviation report had been submitted to the IIRB. No further documentation has been provided to EPA.

The characterization of the deviation as inadvertent is borne out by the correction of the problem on the second day of field testing. I defer to the science reviewer to assess the implications of this deviation on the resulting data concerning protection times. It had no impact on the health or safety of the subjects, and did not compromise the integrity of the consent process.

Applicable Ethical Standards

Because this study was initiated after April 7, 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 May 24, 2007, EPA called for correction of the three ethical deficiencies listed below. The investigator's responses are characterized in italics.

- Although additional inclusion factors are defined for the "experienced" subjects who will serve as untreated controls, the protocol does not describe how they will be recruited, or how the process of informing them and obtaining their consent to this special role in the research will differ from the process used for the treated subjects.

  Addressed satisfactorily in Amendment 1 of June 8, 2007 (see items #5 and #6 on pp. 174-5). This amendment was approved by the IIRB, Inc., on June 12, 2007 and reviewed by HSRB at its meeting in June 2007.

- It is stated erroneously on p. 7 that the concentrations of the active ingredient are lower than in other picaridin products previously registered by EPA. In fact, the concentrations of the active ingredient in the test materials are ***higher*** than in other registered picaridin products.

  Addressed unsatisfactorily in Amendment 1 of June 8, 2007. Further corrected in Amendment 2 of August 14, 2007, not received by IIRB, Inc., at that time, and approved by IIRB, Inc., only on July 21, 2008.

- The data collection forms should be modified to delete the subject's name, and refer to subjects only by their coded ID to protect their privacy.

  Addressed satisfactorily in Amendment 1 of June 8, 2007 (see item #9 on p. 176). This amendment was approved by the IIRB, Inc., on June 12, 2007 and reviewed by HSRB at its meeting in June 2007.

The protocol LNX-001 was presented to the HSRB on June 27, 2007. In the 18 December 2007 final report of its discussion of LNX-001 at its meeting in June, 2007 the HSRB concluded:

> The Board concurred with the assessment of the Agency that the protocol LNX-001 submitted for review by the Board, if revised as suggested in EPA's review, meets the applicable requirements of 40 CFR 26, subparts K and L. In addition, with the submission of the amended protocol, the Board believed that the protocol meets the applicable requirements of 40 CFR 26, subparts K and L.

Regulatory and Statutory Standards

Because this research was initiated after April 7, 2006, 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 suggestions*

  Comments by EPA in its review of 24 May 2007 were addressed in amendment 1 of 8 June 2008, considered by the HSRB at its meeting on June 27, and in amendment 2 of 14 August 2008.

  The HSRB offered no recommendations for further changes.

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

  The requirement of 40 CFR §26.1703 prohibiting research involving intentional exposure of pregnant or nursing women or of children under 18 was met.

- *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 applicable to the conduct of third-party research.

  The record shows that the investigators deviated from the protocol in multiple ways. Three of the four noted deviations were inadvertent errors, noted only after the fact. One reported deviation was, however, a planned change to the protocol, not required to eliminate an apparent immediate hazard to subjects, and should therefore have been approved by the IRB before implementation. The procedures of the IIRB, Inc., required by 40 CFR §26.1108(a)(3) and (4) were ineffective in preventing this change to approved research without IRB approval, nor did the IIRB, Inc., in accepting the report of deviation (p. 282), appear to notice that the change to reliance on previous measurements on file should have been handled as an amendment. This change to the protocol did not put subjects at risk, or compromise the consent process, or affect the integrity of the collected data. But it reflects an apparent misunderstanding by both the investigator and IIRB, Inc., of the obligations of the investigators and IRB with respect to making changes to IRB-approved research.

The record also demonstrates, however, a careful effort by the investigator to incorporate into the LNX-001 protocol and consent forms refinements based on insights gleaned from EPA and HSRB reviews of other similar protocols, and on recommendations of CDPR. During the conduct of the study the investigators consulted assiduously with the IIRB concerning how best to handle problems as they arose, and followed the advice provided by the IIRB. Taking these evidences of a sincere effort to comply with the regulations into account, the noted deficiencies in the conduct of the research do not, in my judgment, rise to the level of substantial non-compliance with subparts A through L of 40 CFR part 26.

- *Compliance with 40 CFR §26 subpart M*

  As is documented in Attachment 1 to this memorandum, the submission of August 12, 2008 fails to address the requirement of 40 CFR §26 subpart M, §26.1303(a) to submit minutes of all IRB meetings at which the research was discussed. Because the letters notifying the investigators of IIRB, Inc. approvals consistently reported unanimous action by the IIRB, this did not compromise EPA's ability to review the research. The record also may omit one IRB review cycle associated with review of changes to the consent forms requested by CDPR. Since a subsequent review cycle is fully documented, this is a minor omission. The remaining requirements of 40 CFR §26.1303 for documentation of the ethical conduct of this research have been met.

- *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. The reporting was incomplete in minor ways that did not compromise the ability to perform a thorough review. 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-001
Attachment 2: Annotated Contents of Appendix 7: LNX-001

§26.1303 Submission of Completed Human Research for EPA Review
LNX-001 (MRID 47506401)

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	Initially addressed with protocol submission; amendments pp. 174-180. Approved CFs pp. 182-200. Progress report p. 268. Report of injury to subject pp. 239-244
	§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	Initially satisfied with protocol submission; No minutes of subsequent IIRB, Inc. discussions of LNX-001 amendments or reports.
	§1115(a)(3): Records of continuing review activities.		Y	pp. 267-271
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.		Y	pp. 208-282
	§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	Satisfied with protocol submission
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).		Y	Previously submitted to EPA
	§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 with protocol submission
		(2) The measures proposed to minimize risks to the human subjects;	Y	
		(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue;	Y	
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	
		(5) The balance of risks and benefits of the proposed research.	Y	
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	Originals in protocol; revisions pp. 249-266; approved pp. 182-200
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	Revised in Amendments 1 and 3 pp. 176-180.
	§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	Revised in Amendments 1 and 3 pp. 176-180.
	§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	Initial approval previously submitted. Approvals of Amendments pp. 181, 201, 202
(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. 182-200
(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	Failure to include IIRB meeting minutes is not explained

Annotated Contents: Appendix 7: Study Protocol and Informed Consent

Pages	Contents
126-127	4/24/08 "Synopsis" of Protocol at time of final amendments
128-167	LNX-001 protocol incorporating amendments 1-3
168	Note referring to location of sponsor signatures on amendments 1-3
169-173	"Study-specific instructions" to IIRB, Inc. (Signed 3/27/07; part of initial application to IIRB, Inc.)
174-176	Amendment #1 8 June 2007 responding to EPA protocol review
177	Amendment #2 14 August 2007 correcting error in Amendment #1
178-180	Amendment #3 25 April 2008 and revised CFs
181	IIRB, Inc. 28 April 2008 approval of Amendment #3 and CFs
182-190	Final Consent Form for treated subjects approved by IIRB, Inc. 29 April 2008
191-200	Final Consent Form for untreated subjects approved by IIRB, Inc. 29 April 2008
201	IIRB, Inc. 12 June 2007 approval of Amendment #1 and revised CFs
202-203	IIRB, Inc. 21 July 2008 approval of Amendment #2
204-205	25 January 2008 Letter of approval by California Department of Pesticide Regulation, citing IIRB approval of 23 October 2007
206-207	Summary of reported deviations
208-247	E-mail CLBR↔IIRB without attachments:
208-213	Re: initial review (3/28/07-4/10/07)
214-217	Re: Amendment 1 (6/8/07-6/13/07)
218-220	Re: Amendment 2 (8/15/07-8/17/07)
221-225	Re: CDPR review and request for changes in CFs. (10/21/07) [Revised consent forms pp. 249-266)]
225-227	Re: Progress report and request for renewal (3/23-24/08). [Progress report p. 268]
227-230	Re: Deviation: Researcher failed to sign consent form (3/31/08-4/1/08). [Deviation report on p. 269]
231	Transmittal of Amendment 3 to IIRB (4/25/08)
232-234	Re: amending CF to express hours to call IIRB in CF in Pacific Time (5/20/08)
235-239	Re: "failure to sign CF" deviation (5/21/08-6/9/08) [cited attachments (5/21/08-6/9/08)
239-244	Re: "minor medical problem" with subject on June 7, 2008 (6/10-30/08)
244-247	Transmittals of various documents (7/14-21/08)
248	Transmittal of Protocol Amendment #1 and revised CFs to EPA (6/14/07). [Attachments not included.]

249-266	Revised CFs as recommended by CDPR and transmitted to IIRB, Inc. (10/21/07)
267	IIRB, Inc. 3/18/08 letter concerning expiration of approval, cited in email p. 225
268	Progress report (3/23/08) cited in email on p. 226
269	Deviation report (3/31/08) cited in email on p. 230
270	IIRB, Inc. letter (4/1/08) approving renewal until 3/31/09
271	IIRB, Inc. letter (4/4/08) accepting deviation report of 3/31/08
272-3	CLBR 4/25/08 letter transmitting protocol amendment #3 and revised CFs to IIRB, Inc.
274	Administrative letter to IIRB (6/5/08) concerning failure to sign CF, cited in emails on p. 238
275	IIRB, Inc. letter (6/9/08) accepting 6/5/08 administrative letter; misidentified in subject line as response to "site letter"
276-277	Deviation report (7/6/08) concerning use of previously collected measurements of subject limbs, transmitted to IIRB, Inc. by 7/16/08 email on p. 245
278	Administrative letter to IIRB (7/16/08) reporting on growth of CLBR subject database from 58 to 112 people, with new demographic data.
279	IIRB, Inc., 7/21/08 acknowledgement of 7/16/08 administrative letter
280-281	Deviation report (7/20/08) concerning failure to ensure IRB approval of Amendment #2
282	IIRB, Inc. 7/21/08 acceptance of deviation reports of 7/6/08 and 7/20/08